L Number	Hits	Search Text	DB	Time stamp
1	29	13-hode or (13hydroxyoctadecadienoic adj acid) or ((coriolic or artemisolic)adj acid) or 13-hydroxyoctadeca-9,11-dienoic	USPAT; US-PGPUB	2002/08/15 12:33
2	32283	linoleic or (ethyl adj oleate) or (ethyl adj linoleate) or (ethyl adj arachidonate) or (docosahexaenoic) or eicosapentaenoic or linolenate or eicosapentaenoate or stearidonate or epa or dha or ethyl-dha or ethyl-epa	USPAT; US-PGPUB	2002/08/15 12:36
3	7587	arachidonic or eicosapentaenoic or dihomogammalinolenic or dhla or alphalinolenic	USPAT; US-PGPUB	2002/08/15 12:36
4	36598	(linoleic or (ethyl adj oleate) or (ethyl adj linoleate) or (ethyl adj arachidonate) or (docosahexaenoic) or eicosapentaenoic or linolenate or eicosapentaenoate or stearidonate or epa or dha or ethyl-dha or ethyl-epa) or (arachidonic or eicosapentaenoic or dihomogammalinolenic or dhla or alphalinolenic)	USPAT; US-PGPUB	2002/08/15 12:37
5	21	(13-hode or (13hydroxyoctadecadienoic adj acid) or ((coriolic or artemisolic)adj acid) or 13-hydroxyoctadeca-9,11-dienoic) and ((linoleic or (ethyl adj oleate) or (ethyl adj linoleate) or (ethyl adj arachidonate) or (docosahexaenoic) or eicosapentaenoic or linolenate or eicosapentaenoate or stearidonate or epa or dha or ethyl-dha or ethyl-epa) or (arachidonic or eicosapentaenoic or dihomogammalinolenic or dhla or alphalinolenic))	USPAT; US-PGPUB	2002/08/15 12:37
6	190	omega-3 adj (fa or (fatty adj acid))	USPAT; US-PGPUB	2002/08/15 12:38
7	29	(13-hode or (13hydroxyoctadecadienoic adj acid) or ((coriolic or artemisolic)adj acid) or 13-hydroxyoctadeca-9,11-dienoic) and (13-hode or (13hydroxyoctadecadienoic adj acid) or ((coriolic or artemisolic)adj acid) or 13-hydroxyoctadeca-9,11-dienoic)	USPAT; US-PGPUB	2002/08/15 12:38
8	2	(13-hode or (13hydroxyoctadecadienoic adj acid) or ((coriolic or artemisolic)adj acid) or 13-hydroxyoctadeca-9,11-dienoic) and (omega-3 adj (fa or (fatty adj acid)))	USPAT; US-PGPUB	2002/08/15 12:38

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     (FILE 'HOME' ENTERED AT 11:38:36 ON 15 AUG 2002)

     FILE 'REGISTRY' ENTERED AT 11:38:56 ON 15 AUG 2002
L1             1 S OMEGA-3 FATTY ACIDS
L2             0 S ETHYL-EPA
L3             0 S  ETHYL EPA
L4            80 S EPA
L5            50 S DHA

     FILE 'CAPLUS' ENTERED AT 11:42:08 ON 15 AUG 2002
L6             1 S WO2001076568/PN
                 SELECT L6 1 RN
L7         10001 S E1-E4,E8,E10,E12-E16
L8           329 S E9 OR 13-HODE
L9            12 S L7 AND L8
L10           12 DUP REM L9 (0 DUPLICATES REMOVED)

     FILE 'MEDLINE, EMBASE, BIOSIS, USPATFULL' ENTERED AT 12:01:28 ON 15 AUG
     2002
L11            3 S L9
L12            3 DUP REM L11 (0 DUPLICATES REMOVED)

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11 ANSWER 3 OF 4 EMBASE COPYRIGHT 2002 ELSEVIER SCI. B.V.
ACCESSION NUMBER: 2000347878 EMBASE
TITLE: Mechanism for the antitumor and anticachectic effects of n-3 fatty acids.
AUTHOR: Saner L.A.; Dauchy R.T.; Blask D.E.
CORPORATE SOURCE: L.A. Saner, Bassett Research Institute, One Atwell Road, Cooperstown, NY 13326, United States. lensauer@juno.com
SOURCE: Cancer Research, (15 Sep 2000) 60/18 (5289-5295).
Refs: 54
ISSN: 0008-5472 CODEN: CNREA8
COUNTRY: United States
DOCUMENT TYPE: Journal; Article
FILE SEGMENT: 016 Cancer
029 Clinical Biochemistry
LANGUAGE: English
SUMMARY LANGUAGE: English

AB Dietary intake of the n-6 fatty acid (FA) **linoleic** acid (LA) has a strong growth-promoting effect on many rodent tumors and human tumor xenografts grown in immunodeficient rodents. n-3 FAs such as .**alpha**.-**linolenic** and eicosapentaenoic acids (EPAs), which differ from LA and arachidonic acid, respectively, by only a single double bond in the n-3 position, are recognized cancer chemopreventive and anticachectic agents. Understanding how this seemingly small structural difference leads to such remarkable functional differences has been a challenge. In a previous study, we showed that LA uptake, [3H]thymidine incorporation into DNA, and total DNA content were decreased in tissue-isolated hepatoma 7288CTC perfused in situ with arterial blood containing .**alpha**.-**linolenic** acid, EPA, or docosahexaenoic acids. The K(i) for the inhibition of LA uptake and [3H]thymidine incorporation by .**alpha**.-**linolenic** acid was 0.18 and 0.25 mM, respectively. Here we show that the addition of .**alpha**.-**linolenic** acid or EPA to arterial blood inhibits tumor FA uptake, including LA, and the subsequent conversion of LA to the mitogen 13-hydroxyoctadecadienoic acid (**13-HODE**) in vivo and during perfusion in situ. [3H]Thymidine incorporation during perfusion in situ was also inhibited. Addition of **13-HODE** to the arterial blood reversed the inhibition of [3H]thymidine incorporation but had no effect on FA uptake. These two n-3 FAs also inhibited FA transport in inguinal fat pads in vivo and during perfusion in situ in fed (FA uptake) and tasted (FA release) rats. The effects of EPA and .**alpha**.-**linolenic** acid on transport of saturated, monounsaturated, and n-6 poly-unsaturated FAs in hepatoma 7288CTC and inguinal fat pads during perfusion in situ were reversed by the addition of forskolin (1 .mu.M), pertussis toxin (0.5 .mu.g/ml), or 8-bromo-cyclic AMP (10 .mu.M) to the arterial blood. We conclude that the antitumor and anticachectic effects of n-3 FAs on hepatoma 7288CTC and inguinal fat pads in vivo result from an inhibition of FA transport. These inhibitions are mediated by a putative n-3 FA receptor via a G(i) protein-coupled signal transduction pathway that decreases intracellular cyclic AMP. A specific decrease in LA uptake and its conversion to the mitogen **13-HODE** causes the tumor growth inhibition.

L11 ANSWER 2 OF 4 CAPLUS COPYRIGHT 2002 ACS
ACCESSION NUMBER: 1990:197018 CAPLUS
DOCUMENT NUMBER: 112:197018
TITLE: Induction of epidermal hyperproliferation by topical n-3 polyunsaturated fatty acids on guinea pig skin linked to decreased levels of 13-hydroxyoctadecadienoic acid (**13-HODE**)
AUTHOR(S): Miller, Craig C.; Ziboh, Vincent A.
CORPORATE SOURCE: Sch. Med., Univ. California, Davis, CA, 95616, USA
SOURCE: J. Invest. Dermatol. (1990), 94(3), 353-8
CODEN: JIDEAE; ISSN: 0022-202X
DOCUMENT TYPE: Journal
LANGUAGE: English

AB Reversal of essential fatty acid deficiency (EFA)-induced epidermal hyperproliferation was recently suggested to require **linoleic** acid and an active lipoxygenase product. Because the nature of this lipoxygenase product is unknown, a model of n-3 polyunsatd. fatty acid (PUFA)-induced hyperproliferation in guinea pig skin was employed to test a possible reversal of the hyperproliferation by an oxidative metabolite of **linoleic** acid. Topical applications of two n-3 PUFA, 0.5% of eicosapentaenoic acid (20:5n-3) and(or) of docosahexaenoic acid (22:6n-3) for 5 days induced severe epidermal hyperproliferation. Development of the epidermal hyperproliferation paralleled a marked decrease in the major epidermal **linoleic** acid lipoxygenase product, **13-HODE**. The application of 0.1% of **13-HODE** to the n-3 PUFA-induced guinea pig hyperproliferative skin resulted in the restoration of normal epidermal histol. and reversal of hyperproliferation as detd. by epidermal uptake of 3H-thymidine. These data support the view that **13-HODE** may represent the endogenous cutaneous mediator necessary for full restoration of cutaneous symptoms of essential fatty acid deficiency. Furthermore, the topical use of n-3 PUFA for the disruption of normal metab. of skin n-6 EFA (**linoleic** acid) does serve as a useful tool for further investigations into the regulatory mechanisms of in vivo epidermal proliferation/differentiation.

IT **18104-45-5**
RL: FORM (Formation, nonpreparative)

L9 ANSWER 7 OF 11 EMBASE COPYRIGHT 2002 ELSEVIER SCI. B.V.
ACCESSION NUMBER: 93104908 EMBASE
DOCUMENT NUMBER: 1993104908
TITLE: Formation of prostanoids and hydroxy fatty acids by stimulated peritoneal mast cells: Role of the dietary fat type in rat.
AUTHOR: Van Haaster C.M.C.J.; Engels W.; Lemmens P.J.M.R.; Hornstra G.; Van der Vusse G.J.
CORPORATE SOURCE: Cardiovascular Research Institute, University of Limburg, P.O. Box 616,6200 MD Maastricht, Netherlands
SOURCE: Biochimica et Biophysica Acta - Lipids and Lipid Metabolism, (1993) 1167/2 (147-154).
ISSN: 0005-2760 CODEN: BBLLA6
COUNTRY: Netherlands
DOCUMENT TYPE: Journal; Article
FILE SEGMENT: 029 Clinical Biochemistry
LANGUAGE: English
SUMMARY LANGUAGE: English
AB To study the influence of membrane fatty acid composition on the formation of prostanoids and hydroxy fatty acids by rat peritoneal mast cells (MC), animals were fed three different types of fatty acids: mackerel oil (MO), abundant in n-3 fatty acids; **sunflower** seed oil (SO), rich in linoleic acid; and hydrogenated coconut oil (HCO), mainly containing saturated fatty acids. The presence of n-3 fatty acids in the diet resulted in the incorporation of 20:5(n-3), 22:5(n-3) and 22:6(n-3) in MC phospholipids. A decrease of arachidonic acid, 20:4(n-6), was observed in MC-phospholipids of the MO-fed animals. Furthermore, increasing the relative amounts of 18:2(n-6) in the diet (SO group) led to an increased incorporation of linoleic acid, 18:2(n-6) in MC phospholipids when compared to both other dietary groups. The changes in MC phospholipid fatty acid composition were (partly) reflected in the formation of prostanoids and hydroxy fatty acids upon stimulation with the calcium ionophore A23187. The decrease in arachidonic acid content in MC phospholipids of MO-fed rats resulted in a decreased formation of PGD2 when compared to both other groups. Also, the increased amounts of 18:2(n-6) in MC phospholipids of SO-fed rats resulted in an increased formation of 9- and **13-HODE** upon stimulation. The results show that modification in the fatty acid composition of the diet influences MC membrane fatty acid composition which ultimately results in changes in prostanoid and hydroxy fatty acid synthesis by MC upon stimulation with the calcium ionophore A23187.

L9 ANSWER 8 OF 11 CAPLUS COPYRIGHT 2002 ACS

L9 ANSWER 4 OF 11 CAPLUS COPYRIGHT 2002 ACS
ACCESSION NUMBER: 1997:493645 CAPLUS
DOCUMENT NUMBER: 127:175827
TITLE: .gamma.-Linolenic acid-containing diet attenuates bleomycin-induced lung fibrosis in hamsters
AUTHOR(S): Ziboh, Vincent A.; Yun, Monica; Hyde, Dallas M.; Giri, Shri N.
CORPORATE SOURCE: Department of Dermatology, School of Medicine, University of California-Davis, Davis, CA, 95616, USA
SOURCE: Lipids (1997), 32(7), 759-767
CODEN: LPDSAP; ISSN: 0024-4201
PUBLISHER: AOCS Press
DOCUMENT TYPE: Journal
LANGUAGE: English

AB Bleomycin (BLM) is used in the treatment of tumors, but the mechanism(s) that contribute to BLM-induced lung injury and fibrosis are not fully elucidated. Since alterations in the levels of certain fatty acid metabolites have been assocd. with BLM-induced lung injury, we tested the effects of dietary .gamma.-linolenic acid (GLA)-contg. **evening primrose** oil on BLM-induced morphol. alterations in the hamster lung, the marked elevation of tissue hydroxyproline (a marker of collagen synthesis), and elevated generation of arachidonic acid metabolites (marker of inflammatory mediators). After 14 d of dietary GLA-contg. oil treatment the BLM-induced elevation of lung hydroxyproline was suppressed and the BLM-induced elevation of lung leukotriene B4 (LTB4) (a marker of polymorphonuclear generation of proinflammatory LTB4) was suppressed. The decrease in LTB4 was accompanied by marked elevations of lung prostaglandin E1 (PGE1) and 15-hydroxyeicosatrienoic acid (15-HETrE), both with known antiinflammatory properties. Thus, GLA-contg. oil in diet contributes to tissue elevation of PGE1 and 15-HETrE, which in vivo may attenuate the lung inflammation and fibrosis.

IT **18104-45-5, 13-Hode**
RL: BPR (Biological process); BSU (Biological study, unclassified); MFM (Metabolic formation); BIOL (Biological study); FORM (Formation, nonpreparative); PROC (Process)
(diet with .gamma.-linolenic acid attenuates bleomycin-induced lung fibrosis in hamsters)

L9 ANSWER 1 OF 11 CAPLUS COPYRIGHT 2002 ACS
ACCESSION NUMBER: 2001:762793 CAPLUS
DOCUMENT NUMBER: 135:308908
TITLE: 13-Hydroxyoctadeca-9Z,11E-dienoic acid as a regulator of vascular biocompatibility and an inhibitor of cell hyperplasia
INVENTOR(S): Buchanan, Michael R.; Horrobin, David
PATENT ASSIGNEE(S): 1411198 Ontario Limited, Can.
SOURCE: PCT Int. Appl., 50 pp.
CODEN: PIXXD2
DOCUMENT TYPE: Patent
LANGUAGE: English
FAMILY ACC. NUM. COUNT: 1
PATENT INFORMATION:

PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
WO 2001076568	A2	20011018	WO 2001-CA477	20010406
W: AE, AG, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, BZ, CA, CH, CN, CO, CR, CU, CZ, DE, DK, DM, DZ, EE, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MA, MD, MG, MK, MN, MW, MX, MZ, NO, NZ, PL, PT, RO, RU, SD, SE, SG, SI, SK, SL, TJ, TM, TR, TT, TZ, UA, UG, US, UZ, VN, YU, ZA, ZW, AM, AZ, BY, KG, KZ, MD, RU, TJ, TM				
RW: GH, GM, KE, LS, MW, MZ, SD, SL, SZ, TZ, UG, ZW, AT, BE, CH, CY, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE, TR, BF, BJ, CF, CG, CI, CM, GA, GN, GW, ML, MR, NE, SN, TD, TG				
US 2002028848	A1	20020307	US 2001-833257	20010409

PRIORITY APPLN. INFO.: CA 2000-2304906 A 20000407

AB This invention relates to the regulation of vascular endothelium biocompatibility and to the inhibition of vessel wall cell and other types of cell hyperplasia following vessel wall dysfunction and/or injury. More particularly, the invention relates to the dietetic and pharmaceutical prepns. of 13-hydroxyoctadeca-9Z,11E-dienoic acid (**13-HODE**) and its use in reducing or inhibiting vessel wall hyperplasia and restoring vessel wall biocompatibility. **13-HODE** (50 mg) is mixed with 450 mg **corn** oil in a soft gelatin or bonded hard gelatin capsule, or 5 mg can be mixed with 100 mg **evening primrose** oil or any other appropriate oil in similar types of capsules.

IT **18104-45-5**
RL: BAC (Biological activity or effector, except adverse); BPR (Biological process); BSU (Biological study, unclassified); THU (Therapeutic use); BIOL (Biological study); PROC (Process); USES (Uses)
(hydroxyoctadecadienoic acid as regulator of vascular biocompatibility and inhibitor of cell hyperplasia)

L9 ANSWER 2 OF 11 CAPLUS COPYRIGHT 2002 ACS
ACCESSION NUMBER: 2000:614316 CAPLUS
DOCUMENT NUMBER: 133:281065
TITLE: Dietary supplementation with a mixture of structured triacylglycerols 1,2,3-tri-.gamma.-linolenylglycerol and 1,2-di-.gamma.-linolenyl-3-mono-oleoylglycerol enhances kidney phospholipid DGLA and prostaglandin E1
AUTHOR(S): Pham, H. T.; Yun, M.; Xi, S.; Ziboh, V. A.
CORPORATE SOURCE: Department of Dermatology, School of Medicine, University of California, Davis, CA, 95616, USA
SOURCE: Nutrition Research (New York) (2000), 20(8), 1151-1161
CODEN: NTRSDC; ISSN: 0271-5317
PUBLISHER: Elsevier Science Inc.
DOCUMENT TYPE: Journal

LANGUAGE: English

AB Investigations involving dietary polyunsatd. fatty acids (PUFA) have linked arachidonic acid (AA, C20:4n-6) and its metabolites to the modulation of renal inflammatory processes. To delineate whether the structural positioning of PUFAs on the glycerol backbone of triacylglycerols can influence fatty acid profiles and eicosanoid generation in the kidney, diets with structured triacylglycerols contg. 49.4% 1,2,3-tri-.gamma.-linolenylglycerol (TGLA) or 46.5% 1,2-di-.gamma.-linolenyl-3-mono-oleoylglycerol (DGMO) and **corn** oil control diet contg. trilinoleoylglycerol were fed to normal guinea pigs for 4 wk. The kidneys were then removed for fatty acid and eicosanoid analyses. The data revealed elevated levels of dihomo-.gamma.-linolenic acid (DGLA; C20:3n-6) in the total phospholipids by 15.0% in TGLA and 10.3% in DGMO animals compared to 6% in controls. These elevations parallel decreases of AA by 16% in TGLA, 19% in DGMO, and 26% in control animals. There was increased generation of PGE1 by 77.7% in TGLA and 59.4% in DGMO animals vs. 57.5% in controls. There was enhanced tissue generation of 15-hydroxyeicosatrienoic acid (15-HETrE) by 21.8% in TGLA and 32.2% in DGMO groups vs. 20.2% in controls. Thus, the increased no. of a particular fatty acid on the glycerol backbone of an ingested triacylglycerol may affect the nature of the PUFA incorporated into the phospholipids and the generation of kidney eicosanoids. Dietary supplementation with structured triacylglycerols may offer a suitable approach to modulate tissue PUFA and anti-inflammatory eicosanoid levels.

IT **18104-45-5, 13-Hode**
RL: BPR (Biological process); BSU (Biological study, unclassified); BIOL (Biological study); PROC (Process)
(dietary supplementation with structured triacylglycerols 1,2,3-tri-.gamma.-linolenylglycerol and 1,2-di-.gamma.-linolenyl-3-mono-oleoylglycerol enhances kidney phospholipid dihomo-.gamma.-linolenic acid and PGE1 levels in guinea pigs)

REFERENCE COUNT: 21 THERE ARE 21 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L9 ANSWER 3 OF 11 CAPLUS COPYRIGHT 2002 ACS
ACCESSION NUMBER: 1999:576759 CAPLUS
DOCUMENT NUMBER: 131:204617
TITLE: Topical formulation of the oil-in-water type, comprising galactolipid material as emulsifier, with a prolonged effect of an incorporated active substance
INVENTOR(S): Carlsson, Anders; Ek, Jenny; Herslof, Bengt; Nilsson, Goran
PATENT ASSIGNEE(S): Scotia Lipidteknik AB, Swed.
SOURCE: PCT Int. Appl., 30 pp.
CODEN: PIXXD2
DOCUMENT TYPE: Patent
LANGUAGE: English
FAMILY ACC. NUM. COUNT: 1
PATENT INFORMATION:

PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
WO 9944585	A1	19990910	WO 1999-SE347	19990308

W: AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, CA, CH, CN, CU, CZ, DE, DK, EE, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MD, MG, MK, MN, MW, MX, NO, NZ, PL, PT, RO, RU, SD, SE, SG, SI, SK, SL, TJ, TM, TR, TT, UA, UG, US, UZ, VN, YU, ZW, AM, AZ, BY, KG, KZ, MD, RU, TJ, TM

RW: GH, GM, KE, LS, MW, SD, SL, SZ, UG, ZW, AT, BE, CH, CY, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE, BF, BJ, CF, CG, CI, CM, GA, GN, GW, ML, MR, NE, SN, TD, TG

SE 9800729	A	19990907	SE 1998-729	19980306
CA 2322850	AA	19990910	CA 1999-2322850	19990308
AU 9931778	A1	19990920	AU 1999-31778	19990308
EP 1069886	A1	20010124	EP 1999-913784	19990308
R: AT, BE, CH, DE, DK, ES, FR, GB, GR, IT, LI, LU, NL, SE, PT, IE, FI				
JP 2002505272	T2	20020219	JP 2000-534188	19990308

PRIORITY APPLN. INFO.: SE 1998-729 A 19980306
WO 1999-SE347 W 19990308

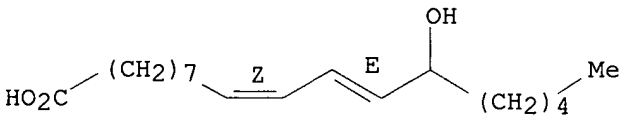
AB The invention relates to the use of a topical formulation of the oil-in-water type comprising an oily material, an aq. phase and an emulsifier, wherein the emulsifier is a galactolipid material, as a carrier for providing a prolonged effect of an incorporated active substance. New topical formulations are also described. An anti-inflammatory cream contained betamethasone dipropionate 0.05, CPL-**evening primrose** oil 20, cetostearyl alc. 7, glyceryl monostearate 2, ascorbyl palmitate 0.02, CPL-galactolipid 1.5, glycerol 2, methylparaben 0.63, propylparaben 0.07, and water q.s. to 100 %.

IT **18104-45-5, 13-HODE**
RL: THU (Therapeutic use); BIOL (Biological study); USES (Uses)
(oil-in-water topical prepns. contg. galactolipids as emulsifiers)

REFERENCE COUNT: 2 THERE ARE 2 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L1 ANSWER 2 OF 2 REGISTRY COPYRIGHT 2002 ACS
RN 18104-45-5 REGISTRY
CN 9,11-Octadecadienoic acid, 13-hydroxy-, (9Z,11E)- (9CI) (CA INDEX NAME)
OTHER CA INDEX NAMES:
CN 9,11-Octadecadienoic acid, 13-hydroxy-, (E,Z)- (8CI)
OTHER NAMES:
CN (.+-.)-Coriolic acid
CN (9Z,11E)-13-Hydroxy-9,11-octadecadienoic acid
CN .alpha.-Artemisolic acid
CN **13-HODE**
CN 13-Hydroxy-9,11-cis,trans-octadecadienoic acid
CN 13-Hydroxy-9-cis-11-trans-octadecadienoic acid
CN 13-Hydroxy-cis-9-trans-11-octadecadienoic acid
CN 13-Hydroxyoctadeca-9,11-dienoic acid
FS STEREOSEARCH
DR 73804-64-5, 81445-95-6
MF C18 H32 O3
LC STN Files: AGRICOLA, BEILSTEIN*, BIOSIS, CA, CAPLUS, CASREACT, CHEMCATS, CHEMINFORMRX, CSCHEM, TOXCENTER, USPATFULL
(*File contains numerically searchable property data)

Double bond geometry as shown.



PROPERTY DATA AVAILABLE IN THE 'PROP' FORMAT

237 REFERENCES IN FILE CA (1967 TO DATE)
2 REFERENCES TO NON-SPECIFIC DERIVATIVES IN FILE CA
238 REFERENCES IN FILE CAPLUS (1967 TO DATE)

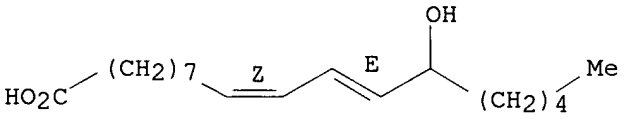
L4 ANSWER 19 OF 44 CAPLUS COPYRIGHT 2002 ACS
ACCESSION NUMBER: 1998:43561 CAPLUS
DOCUMENT NUMBER: 128:165533
TITLE: Upregulation of nuclear PKC and MAP-kinase during hyperproliferation of guinea pig epidermis: modulation by 13-(S)-hydroxyoctadecadienoic acid (13-HODE)
AUTHOR(S): Mani, Indu; Iversen, Lars; Ziboh, Vincent A.
CORPORATE SOURCE: Department of Dermatology, University of California, Davis, CA, 95616, USA
SOURCE: Cellular Signalling (1998), 10(2), 143-149
CODEN: CESIEY; ISSN: 0898-6568
PUBLISHER: Elsevier Science Inc.
DOCUMENT TYPE: Journal
LANGUAGE: English

AB 13-(S)-Hydroxyoctadecadienoic acid (13-HODE), the lipoxygenase metabolite of linoleic acid, has been shown to reverse the epidermal hyperproliferation induced by topical application of docosahexaenoic acid (DHA, 22:6 n-3) on guinea pig skin. Our initial studies demonstrated that 13-HODE exerts a selective inhibition of the membrane-bound PKC-.beta. activity in the hyperproliferative skin. To delineate the antiproliferative effects of 13-HODE, we investigated the nuclear events assocd. with this process. Our data demonstrated that the major PKC isoenzymes in the epidermal nuclear fraction are .alpha. and .zeta.. Epidermal hyperproliferation induced by DHA caused an increase in nuclear total PKC and atypical PKC activities, and this was accompanied by an increase in the two nuclear isoenzymes, .alpha. and .zeta. ($P < 0.05$). This increase was reversed after topical application of 13-HODE. Similarly, 13-HODE suppressed elevated nuclear MAP-kinase. Taken together, these data suggest that nuclear signalling events in the epidermis involve PKC-MAP-kinase pathway.

IT **18104-45-5**, 13-HODE
RL: BAC (Biological activity or effector, except adverse); BSU (Biological study, unclassified); BIOL (Biological study)
(upregulation of nuclear PKC and MAP-kinase during hyperproliferation of guinea pig epidermis, and its modulation by 13-(S)-hydroxyoctadecadienoic acid)

RN 18104-45-5 CAPLUS
CN 9,11-Octadecadienoic acid, 13-hydroxy-, (9Z,11E)- (9CI) (CA INDEX NAME)

Double bond geometry as shown.



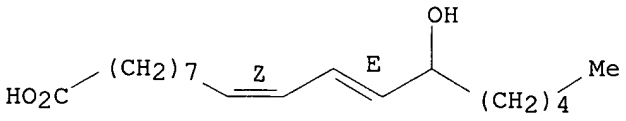
CCESSION NUMBER: 1998:375522 CAPLUS
DOCUMENT NUMBER: 129:159742
TITLE: Effects of 13-HODE and other monohydroxides on integrin/ligand binding: implications for cell cell interactions
AUTHOR(S): Buchanan, M. R.; Brister, S. J.
CORPORATE SOURCE: Department of Pathology, McMaster University, Hamilton, ON, L8L 8E7, Can.
SOURCE: Advances in Experimental Medicine and Biology (1997), 433(Recent Advances in Prostaglandin, Thromboxane, and Leukotriene Research), 265-269
CODEN: AEMBAP; ISSN: 0065-2598
PUBLISHER: Plenum Publishing Corp.
DOCUMENT TYPE: Journal
LANGUAGE: English

AB It is suggested that regulation of cell integrin adhesivity by lipoxygenase derived monohydroxides is a common mechanism in vascular and circulating blood cells. If so, modulating 13-HODE and other monohydroxides synthesis under basal and stimulated **conditions** in vivo may be a useful approach to altering cell cell-mediated outcome events in the clin. situation.

IT **18104-45-5**, 13-HODE
RL: BAC (Biological activity or effector, except adverse); BSU (Biological study, unclassified); BIOL (Biological study)
(effects of 13-HODE and other monohydroxides on integrin/ligand binding in cell/cell interactions)

RN 18104-45-5 CAPLUS
CN 9,11-Octadecadienoic acid, 13-hydroxy-, (9Z,11E)- (9CI) (CA INDEX NAME)

Double bond geometry as shown.



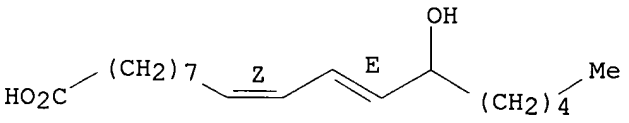
L4 ANSWER 12 OF 44 CAPLUS COPYRIGHT 2002 ACS
ACCESSION NUMBER: 2000:235404 CAPLUS
DOCUMENT NUMBER: 133:767
TITLE: Suppression of proto-oncogene (AP-1) in a model of skin epidermal hyperproliferation is reversed by topical application of 13-hydroxyoctadecadienoic acid and 15-hydroxyeicosatrienoic acid
AUTHOR(S): Xi, S.; Pham, H.; Ziboh, V. A.
CORPORATE SOURCE: Department of Dermatology, School of Medicine, University of California at Davis, Davis, CA, 95616, USA
SOURCE: Prostaglandins, Leukotrienes and Essential Fatty Acids (2000), 62(1), 13-19
CODEN: PLEAEU; ISSN: 0952-3278
PUBLISHER: Churchill Livingstone
DOCUMENT TYPE: Journal
LANGUAGE: English

AB The present study was conducted to delineate whether a possible mechanism for 13-(S)-hydroxyoctadecadienoic acid (13-HODE) and 15-hydroxyeicosatrienoic acid (15-HETrE) reversal of exptl.-induced skin hyperproliferation in guinea pig is via the modulation of epidermal nuclear mitogen activator protein (AP-1), a nuclear transcription factor assocd. with tissue turnover. The data revealed that topical application of 13-HODE and/or 15-HETrE on the induced hyperproliferative skin reversed the hyperproliferation and up-regulated the suppressed AP-1 expression. A further anal. of the two major subunits of AP-1 (c-fos and c-jun) revealed a selective up-regulation of c-fos. These results underscore the modulatory role of lipoxygenase-derived hydroxy fatty acids on nuclear transcription factors and explains, at least in part, the antiproliferative effects of 13-HODE and 15-HETrE.

IT **18104-45-5**, 13-HODE
RL: BAC (Biological activity or effector, except adverse); BSU (Biological study, unclassified); BIOL (Biological study)
(suppression of proto-oncogene (AP-1) in a model of skin epidermal hyperproliferation is reversed by topical application of 13-hydroxyoctadecadienoic acid and 15-hydroxyeicosatrienoic acid)

RN 18104-45-5 CAPLUS
CN 9,11-Octadecadienoic acid, 13-hydroxy-, (9Z,11E)- (9CI) (CA INDEX NAME)

Double bond geometry as shown.



L12 ANSWER 2 OF 3 BIOSIS COPYRIGHT 2002 BIOLOGICAL ABSTRACTS INC.
ACCESSION NUMBER: 1996:243967 BIOSIS
DOCUMENT NUMBER: PREV199698792096
TITLE: The significance of polyunsaturated fatty acids in cutaneous biology.
AUTHOR(S): Ziboh, Vincent A.
CORPORATE SOURCE: Dep. Dermatol., Univ. California, Davis, CA USA
SOURCE: Lipids, (1996) Vol. 31, No. SUPPL., pp. S249-S253. ISSN: 0024-4201.
DOCUMENT TYPE: Article
LANGUAGE: English

AB The skin epidermis displays a highly active metabolism of polyunsaturated fatty acids (PUFA). Dietary deficiency of linoleic acid (LA) and 18-carbon (n-6) PUFA results in characteristic scaly skin disorder and excessive epidermal water loss. Arachidonic acid, a 20-carbon (n-6) PUFA is metabolized via the cyclooxygenase pathway into predominantly prostaglandin E-2 (PGE-2) PGF-2-alpha, and PGD-2 and via the lipoxygenase pathway into predominantly 15-hydroxyeicosatetraenoic acid (15-HETE). The prostaglandins modulate normal skin physiological processes at low concentrations and inflammatory reactions at high concentrations. Similarly, the very active epidermal 15-lipoxygenase transforms dihomogammalinolenic acid (DGLA) into 15-hydroxy eicosatrienoic acid (15-HETrE), eicosapentaenoic acid (EPA) into 15-hydroxyeicosapentaenoic acid (15-HEPE) and docosahexaenoic acid (DHA) into 17-hydroxydocosahexaenoic acid (17-HDoHE), respectively. These monohydroxy acids exhibit anti-inflammatory properties. In contrast, the 18-carbon (n-6) PUFA is transformed into 13-hydroxy-9,11-octadecadienoic acid (**13-HODE**), which exerts antiproliferative properties in the tissue. Thus the supplementation of diets with appropriate purified vegetable oils and/or fish oil may generate local cutaneous anti-inflammatory metabolites which could serve as a less toxic in vivo monotherapy or as adjuncts to standard therapeutic regimens for the management of skin inflammatory disorders.

IT Major Concepts
Biochemistry and Molecular Biophysics; Cell Biology; Dermatology (Human Medicine, Medical Sciences); Metabolism; Nutrition; Pathology

IT Chemicals & Biochemicals
LINOLEIC ACID; ARACHIDONIC ACID; PROSTAGLANDIN F-2ALPHA; PROSTAGLANDIN-D2; 15-HYDROXYEICOSATETRAENOIC ACID; DIHOMOGAMMALINOLENIC ACID; EICOSATRIENOIC ACID; EICOSAPENTAENOIC ACID; DOCOSAHEXAENOIC ACID; 13-HYDROXY-9,11-OCTADECADIENOIC ACID; CYCLOOXYGENASE; LIPOXYGENASE; 15-LIPOXYGENASE

IT Miscellaneous Descriptors
ANTIPROLIFERATION RESPONSE; ARACHIDONIC ACID; CYCLOOXYGENASE; DIETARY SUPPLEMENTATION; DIHOMOGAMMALINOLENIC ACID; DOCOSAHEXAENOIC ACID; EICOSAPENTAENOIC ACID; EPIDERMAL WATER LOSS; FISH OIL; INFLAMMATION; LINOLEIC ACID; LIPOXYGENASE; PROSTAGLANDIN F-2ALPHA; PROSTAGLANDIN-D2; PROSTAGLANDIN-E2; SCALY SKIN DISORDER; VEGETABLE OIL; 13-HYDROXY-9,11-OCTADECADIENOIC ACID; 15-HYDROXY EICOSATRIENOIC ACID; 15-HYDROXYEICOSATETRAENOIC ACID; 15-LIPOXYGENASE; 18-CARBON (N-6) POLYUNSATURATED FATTY ACID

ORGN Super Taxa
Hominidae: Primates, Mammalia, Vertebrata, Chordata, Animalia

ORGN Organism Name
human (Hominidae)

ORGN Organism Superterms
animals; chordates; humans; mammals; primates; vertebrates

RN 60-33-3 (LINOLEIC ACID)
506-32-1 (ARACHIDONIC ACID)
551-11-1 (PROSTAGLANDIN F-2ALPHA)
41598-07-6 (PROSTAGLANDIN-D2)

54845-95-3Q (15-HYDROXYEICOSATETRAENOIC ACID)
71030-36-9Q (15-HYDROXYEICOSATETRAENOIC ACID)
73180-00-4Q (15-HYDROXYEICOSATETRAENOIC ACID)
1783-84-2 (DIHOMOGAMMALINOLENIC ACID)
27070-56-0Q (EICOSATRIENOIC ACID)
80558-45-8Q (EICOSATRIENOIC ACID)
10417-94-4Q (EICOSAPENTAENOIC ACID)
25378-27-2Q (EICOSAPENTAENOIC ACID)
32839-30-8Q (EICOSAPENTAENOIC ACID)
6217-54-5Q (DOCOSAHEXAENOIC ACID)
25167-62-8Q (DOCOSAHEXAENOIC ACID)
32839-18-2Q (DOCOSAHEXAENOIC ACID)
5204-88-6Q (13-HYDROXY-9,11-OCTADECADIENOIC ACID)
18104-45-5Q (13-HYDROXY-9,11-OCTADECADIENOIC ACID)
39391-18-9 (CYCLOOXYGENASE)
9029-60-1Q (LIPOXYGENASE)
63551-74-6Q (LIPOXYGENASE)
82249-77-2 (15-LIPOXYGENASE)

L12 ANSWER 3 OF 3 BIOSIS COPYRIGHT 2002 BIOLOGICAL ABSTRACTS INC.
ACCESSION NUMBER: 1990:179189 BIOSIS
DOCUMENT NUMBER: BA89:96359
TITLE: INDUCTION OF EPIDERMAL HYPERPROLIFERATION BY TOPICAL N-3 POLYUNSATURATED FATTY ACIDS ON GUINEA-PIG SKIN LINKED TO DECREASED LEVELS OF 13 HYDROXYOCTADECADIENOIC ACID **13 HODE**.
AUTHOR(S): MILLER C C; ZIBOH V A
CORPORATE SOURCE: DEP. DERMATOL., TB 192, SCH. MED., UNIV. CALIFORNIA, DAVIS, CALIF. 95616.
SOURCE: J INVEST DERMATOL, (1990) 94 (3), 353-358.
CODEN: JIDEAE. ISSN: 0022-202X.
FILE SEGMENT: BA; OLD
LANGUAGE: English
AB Reversal of essential fatty acid deficiency (EFA) induced epidermal hyperproliferation was recently suggested to require linoleic acid and an active lipoxygenase product. Because the nature of this lipoxygenase product is unknown, we employed a model of n-3 polyunsaturated fatty acid (PUFA) induced hyperproliferation in guinea pig skin to test a possible reversal of the hyperproliferation by an oxidative metabolite of linoleic acid. Topical applications of two n-3 PUFA: 0.5% of eicosapentaenoic acid (20:5n-3) and/or of docosahexaenoic acid (22:6n-3) for 5 d induced severe epidermal hyperproliferation. Development of the epidermal hyperproliferation paralleled a marked decrease in the major epidermal linoleic lipoxygenase product (13-hydroxyoctadecadienoic acid; **13-HODE**). The application of 0.1% of **13-HODE** to the n-3 PUFA-induced guinea pig hyperpoliferative skin resulted in the restoration of normal epidermal histology and reversal of hyprproliferation as determined by epidermal uptake of 3H-thymidine. These data support the view that **13-HODE** may represent the endogenous cutaneous mediator necessary for full restoration of cutaneous symptoms of essential fatty acid deficiency. Furthermore, the topical use of n-3 PUFA for the disruption of normal metabolism of skin n-6 EFA (linoleic acid) does serve as a useful tool for further investigations into the regulatory mechanisms of in vivo epidermal proliferation/differentiation.
IT Miscellaneous Descriptors
LINOLEIC ACID EICOSAPENTAENOIC ACID DOCOSAHEXAENOIC ACID ESSENTIAL FATTY ACID DEFICIENCY
RN 60-33-3 (LINOLEIC ACID)
6217-54-5Q, 25167-62-8Q, 32839-18-2Q (DOCOSAHEXAENOIC ACID)
10417-94-4Q, 25378-27-2Q, 32839-30-8Q (EICOSAPENTAENOIC ACID)

L12 ANSWER 1 OF 3 BIOSIS COPYRIGHT 2002 BIOLOGICAL ABSTRACTS INC.
ACCESSION NUMBER: 2000:487659 BIOSIS
DOCUMENT NUMBER: PREV200000487659
TITLE: Mechanism for the antitumor and anticachectic effects of n-3 fatty acids.
AUTHOR(S): Sauer, Leonard A. (1); Dauchy, Robert T.; Blask, David E.
CORPORATE SOURCE: (1) Bassett Research Institute, One Atwell Road, Cooperstown, NY, 13326 USA
SOURCE: Cancer Research, (September 15, 2000) Vol. 60, No. 18, pp. 5289-5295. print.
ISSN: 0008-5472.
DOCUMENT TYPE: Article
LANGUAGE: English
SUMMARY LANGUAGE: English

AB Dietary intake of the n-6 fatty acid (FA) linoleic acid (LA) has a strong growth-promoting effect on many rodent tumors and human tumor xenografts grown in immunodeficient rodents. n-3 FAs such as alpha-linolenic and eicosapentaenoic acids (EPAs), which differ from LA and arachidonic acid, respectively, by only a single double bond in the n-3 position, are recognized cancer chemopreventive and anticachectic agents. Understanding how this seemingly small structural difference leads to such remarkable functional differences has been a challenge. In a previous study, we showed that LA uptake, (3H)thymidine incorporation into DNA, and total DNA content were decreased in tissue-isolated hepatoma 7288CTC perfused in situ with arterial blood containing alpha-linolenic acid, EPA, or docosahexaenoic acids. The Ki for the inhibition of LA uptake and (3H)thymidine incorporation by alpha-linolenic acid was 0.18 and 0.25 mM, respectively. Here we show that the addition of alpha-linolenic acid or EPA to arterial blood inhibits tumor FA uptake, including LA, and the subsequent conversion of LA to the mitogen 13-hydroxyoctadecadienoic acid (**13-HODE**) in vivo and during perfusion in situ. (3H)Thymidine incorporation during perfusion in situ was also inhibited. Addition of **13-HODE** to the arterial blood reversed the inhibition of (3H)thymidine incorporation but had no effect on FA uptake. These two n-3 FAs also inhibited FA transport in inguinal fat pads in vivo and during perfusion in situ in fed (FA uptake) and fasted (FA release) rats. The effects of EPA and alpha-linolenic acid on transport of saturated, monounsaturated, and n-6 polyunsaturated FAs in hepatoma 7288CTC and inguinal fat pads during perfusion in situ were reversed by the addition of forskolin (1 muM), pertussis toxin (0.5 mug/ml), or 8-bromo-cyclic AMP (10 muM) to the arterial blood. We conclude that the antitumor and anticachectic effects of n-3 FAs on hepatoma 7288CTC and inguinal fat pads in vivo result from an inhibition of FA transport. These inhibitions are mediated by a putative n-3 FA receptor via a Gi protein-coupled signal transduction pathway that decreases intracellular cyclic AMP. A specific decrease in LA uptake and its conversion to the mitogen **13-HODE** causes the tumor growth inhibition.

IT Major Concepts
Tumor Biology
IT Parts, Structures, & Systems of Organisms
inguinal fat pads
IT Diseases
hepatoma: digestive system disease, neoplastic disease
IT Chemicals & Biochemicals
13-hydroxyoctadecadienoic acid: mitogen; alpha-linolenic acid; cyclic AMP: intracellular; eicosapentaenoic acids; n-3 fatty acid receptor; n-3 fatty acids: anticachectic effects, antitumor effects, pharmacodynamics
IT Miscellaneous Descriptors
G-i protein-coupled signal transduction pathway
ORGN Super Taxa
Muridae: Rodentia, Mammalia, Vertebrata, Chordata, Animalia

ORGN Organism Name
rat (Muridae)
ORGN Organism Superterms
Animals; Chordates; Mammals; Nonhuman Mammals; Nonhuman Vertebrates; Rodents; Vertebrates
RN 463-40-1 (ALPHA-LINOLENIC ACID)
60-92-4 (CYCLIC AMP)
10417-94-4Q (EICOSAPENTAENOIC ACIDS)
25378-27-2Q (EICOSAPENTAENOIC ACIDS)
32839-30-8Q (EICOSAPENTAENOIC ACIDS)

L10 12 DUP REM L9 (0 DUPLICATES REMOVED)

=> d ibib abs it 1-12

L10 ANSWER 1 OF 12 CAPLUS COPYRIGHT 2002 ACS
ACCESSION NUMBER: 2001:762793 CAPLUS
DOCUMENT NUMBER: 135:308908
TITLE: 13-Hydroxyoctadeca-9Z,11E-dienoic acid as a regulator of vascular biocompatibility and an inhibitor of cell hyperplasia
INVENTOR(S): Buchanan, Michael R.; Horrobin, David
PATENT ASSIGNEE(S): 1411198 Ontario Limited, Can.
SOURCE: PCT Int. Appl., 50 pp.
CODEN: PIXXD2
DOCUMENT TYPE: Patent
LANGUAGE: English
FAMILY ACC. NUM. COUNT: 1
PATENT INFORMATION:

PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
WO 2001076568	A2	20011018	WO 2001-CA477	20010406
W: AE, AG, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, BZ, CA, CH, CN, CO, CR, CU, CZ, DE, DK, DM, DZ, EE, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MA, MD, MG, MK, MN, MW, MX, MZ, NO, NZ, PL, PT, RO, RU, SD, SE, SG, SI, SK, SL, TJ, TM, TR, TT, TZ, UA, UG, US, UZ, VN, YU, ZA, ZW, AM, AZ, BY, KG, KZ, MD, RU, TJ, TM				
RW: GH, GM, KE, LS, MW, MZ, SD, SL, SZ, TZ, UG, ZW, AT, BE, CH, CY, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE, TR, BF, BJ, CF, CG, CI, CM, GA, GN, GW, ML, MR, NE, SN, TD, TG				
US 2002028848	A1	20020307	US 2001-833257	20010409

PRIORITY APPLN. INFO.: CA 2000-2304906 A 20000407

AB This invention relates to the regulation of vascular endothelium biocompatibility and to the inhibition of vessel wall cell and other types of cell hyperplasia following vessel wall dysfunction and/or injury. More particularly, the invention relates to the dietetic and pharmaceutical prepns. of 13-hydroxyoctadeca-9Z,11E-dienoic acid (**13-HODE**) and its use in reducing or inhibiting vessel wall hyperplasia and restoring vessel wall biocompatibility. **13-HODE** (50 mg) is mixed with 450 mg corn oil in a soft gelatin or bonded hard gelatin capsule, or 5 mg can be mixed with 100 mg evening primrose oil or any other appropriate oil in similar types of capsules.

IT Fats and Glyceridic oils, biological studies
RL: THU (Therapeutic use); BIOL (Biological study); USES (Uses)
(borage seed; hydroxyoctadecadienoic acid as regulator of vascular biocompatibility and inhibitor of cell hyperplasia)

IT Drug delivery systems
(capsules; hydroxyoctadecadienoic acid as regulator of vascular biocompatibility and inhibitor of cell hyperplasia)

IT Brain, disease
(cerebrovascular, inhibitors; hydroxyoctadecadienoic acid as regulator of vascular biocompatibility and inhibitor of cell hyperplasia)

IT Digestive tract
Nervous system
Respiratory tract
Urinary tract
(disease, inhibitors; hydroxyoctadecadienoic acid as regulator of vascular biocompatibility and inhibitor of cell hyperplasia)

IT Cardiovascular system
(disease; hydroxyoctadecadienoic acid as regulator of vascular biocompatibility and inhibitor of cell hyperplasia)

IT Drug delivery systems
(dragees; hydroxyoctadecadienoic acid as regulator of vascular biocompatibility and inhibitor of cell hyperplasia)
IT Blood vessel
(endothelium; hydroxyoctadecadienoic acid as regulator of vascular biocompatibility and inhibitor of cell hyperplasia)
IT Fats and Glyceridic oils, biological studies
RL: THU (Therapeutic use); BIOL (Biological study); USES (Uses)
(evening primrose; hydroxyoctadecadienoic acid as regulator of vascular biocompatibility and inhibitor of cell hyperplasia)
IT Fats and Glyceridic oils, biological studies
RL: THU (Therapeutic use); BIOL (Biological study); USES (Uses)
(fish-liver; hydroxyoctadecadienoic acid as regulator of vascular biocompatibility and inhibitor of cell hyperplasia)
IT Fats and Glyceridic oils, biological studies
RL: THU (Therapeutic use); BIOL (Biological study); USES (Uses)
(fish; hydroxyoctadecadienoic acid as regulator of vascular biocompatibility and inhibitor of cell hyperplasia)
IT Drug delivery systems
(freeze-dried; hydroxyoctadecadienoic acid as regulator of vascular biocompatibility and inhibitor of cell hyperplasia)
IT Drug delivery systems
(granules; hydroxyoctadecadienoic acid as regulator of vascular biocompatibility and inhibitor of cell hyperplasia)
IT Fats and Glyceridic oils, biological studies
RL: THU (Therapeutic use); BIOL (Biological study); USES (Uses)
(grape seed; hydroxyoctadecadienoic acid as regulator of vascular biocompatibility and inhibitor of cell hyperplasia)
IT Anti-inflammatory agents
Antibacterial agents
Antidiabetic agents
Antioxidants
Antitumor agents
Antiviral agents
Biocompatibility
Buffers
Cardiovascular agents
Dyes
Fungicides
Hyperplasia
Protozoacides
Psychotropics
Sweetening agents
(hydroxyoctadecadienoic acid as regulator of vascular biocompatibility and inhibitor of cell hyperplasia)
IT Corn oil
Cottonseed oil
Diglycerides
Glycerides, biological studies
Lecithins
Monoglycerides
Olive oil
Safflower oil
Salts, biological studies
Sunflower oil
Tocopherols
RL: THU (Therapeutic use); BIOL (Biological study); USES (Uses)
(hydroxyoctadecadienoic acid as regulator of vascular biocompatibility and inhibitor of cell hyperplasia)
IT Autoimmune disease
Kidney, disease
Nervous system agents

Skin, disease
(inhibitors; hydroxyoctadecadienoic acid as regulator of vascular biocompatibility and inhibitor of cell hyperplasia)

IT Antitumor agents
(metastasis; hydroxyoctadecadienoic acid as regulator of vascular biocompatibility and inhibitor of cell hyperplasia)

IT Drug delivery systems
(suspensions; hydroxyoctadecadienoic acid as regulator of vascular biocompatibility and inhibitor of cell hyperplasia)

IT Drug delivery systems
(tablets; hydroxyoctadecadienoic acid as regulator of vascular biocompatibility and inhibitor of cell hyperplasia)

IT **18104-45-5**
RL: BAC (Biological activity or effector, except adverse); BPR (Biological process); BSU (Biological study, unclassified); THU (Therapeutic use); BIOL (Biological study); PROC (Process); USES (Uses)
(hydroxyoctadecadienoic acid as regulator of vascular biocompatibility and inhibitor of cell hyperplasia)

IT 142243-02-5, Mitogen-activated protein kinase
RL: BSU (Biological study, unclassified); BIOL (Biological study)
(hydroxyoctadecadienoic acid as regulator of vascular biocompatibility and inhibitor of cell hyperplasia)

IT 50-81-7, Ascorbic acid, biological studies **111-62-6**, Ethyl oleate 137-66-6, Ascorbyl palmitate **544-35-4**, Ethyl linoleate **1808-26-0**, Ethyl arachidonate **6217-54-5**, Docosahexaenoic acid **10417-94-4**, Eicosapentaenoic acid **31450-14-3**, Ethyl .gamma.-linolenate **55968-21-3**, Ethyl dihomo-.gamma.-linolenate **81926-94-5**, Ethyl docosahexaenoate **85354-43-4**, Ethyl eicosapentaenoate **119798-44-6**, Ethyl stearidonate **129698-18-6**
RL: THU (Therapeutic use); BIOL (Biological study); USES (Uses)
(hydroxyoctadecadienoic acid as regulator of vascular biocompatibility and inhibitor of cell hyperplasia)

IT 9026-43-1, Protein kinase 141436-78-4, Protein kinase C
RL: BSU (Biological study, unclassified); BIOL (Biological study)
(inhibitors; hydroxyoctadecadienoic acid as regulator of vascular biocompatibility and inhibitor of cell hyperplasia)

L10 ANSWER 2 OF 12 CAPLUS COPYRIGHT 2002 ACS
ACCESSION NUMBER: 2001:617963 CAPLUS
DOCUMENT NUMBER: 135:190408
TITLE: Aspirin-triggered lipid mediators
INVENTOR(S): Serhan, Charles N.; Clish, Clary B.
PATENT ASSIGNEE(S): The Brigham and Women's Hospital, Inc., USA
SOURCE: PCT Int. Appl., 74 pp.
CODEN: PIXXD2
DOCUMENT TYPE: Patent
LANGUAGE: English
FAMILY ACC. NUM. COUNT: 1
PATENT INFORMATION:

PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
WO 2001060778	A2	20010823	WO 2001-US5196	20010216

W: AE, AG, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, BZ, CA, CH, CN, CR, CU, CZ, DE, DK, DM, DZ, EE, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MA, MD, MG, MK, MN, MW, MX, MZ, NO, NZ, PL, PT, RO, RU, SD, SE, SG, SI, SK, SL, TJ, TM, TR, TT, TZ, UA, UG, UZ, VN, YU, ZA, ZW, AM, AZ, BY, KG, KZ, MD, RU, TJ, TM

RW: GH, GM, KE, LS, MW, MZ, SD, SL, SZ, TZ, UG, ZW, AT, BE, CH, CY, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE, TR, BF,

BJ, CF, CG, CI, CM, GA, GN, GW, ML, MR, NE, SN, TD, TG

US 2002055538 A1 20020509 US 2001-785866 20010216

PRIORITY APPLN. INFO.: US 2000-183078P P 20000216

US 2000-238814P P 20001006

OTHER SOURCE(S): MARPAT 135:190408

AB Aspirin triggered lipid mediators are disclosed which are useful for the treatment or prevention of inflammation assocd. with various diseases, including ischemia. The present invention provides that inflammatory exudates from mice treated with .omega.-3 PUFA and aspirin generate a novel array of bioactive lipid signals. Human endothelial cells with upregulated COX-2 treated with aspirin converted C20:5 w-3 to 18R-HEPE and 15R-HEPE. Each was used by polymorphonuclear leukocytes to generate sep. classes of novel trihydroxy-contg. mediators, including 15R-lipoxin and 5,12,18R-triHEPE. These compds. were potent inhibitors of human polymorphonuclear leukocyte transendothelial migration and infiltration in vivo.

IT Artery, disease
(arteritis; mechanism of inflammation treatment or prevention by .omega.-3 fatty acid and aspirin combination)

IT Bacillus megaterium
(conversion of eicosapentaenoic acid by B. megaterium)

IT Cardiovascular system
(disease; mechanism of inflammation treatment or prevention by .omega.-3 fatty acid and aspirin combination)

IT Exudate
(inflammatory; lipid mediators generated in inflammatory exudate by combination of .omega.-3 PUFA and aspirin)

IT Leukotriene receptors
RL: BPR (Biological process); BSU (Biological study, unclassified); BIOL (Biological study); PROC (Process)
(leukotriene B4; lipid mediators generated by combination of .omega.-3 PUFA and aspirin)

IT Interleukin 3
Tumor necrosis factors
RL: BAC (Biological activity or effector, except adverse); BSU (Biological study, unclassified); BIOL (Biological study)
(lipid mediators generated by combination of .omega.-3 PUFA and aspirin)

IT Lipids, biological studies
RL: BSU (Biological study, unclassified); BIOL (Biological study)
(lipid mediators generated by combination of .omega.-3 PUFA and aspirin)

IT Leukotrienes
RL: FMU (Formation, unclassified); FORM (Formation, nonpreparative)
(lipid mediators generated by combination of .omega.-3 PUFA and aspirin)

IT Prostaglandins
RL: FMU (Formation, unclassified); FORM (Formation, nonpreparative)
(lipid mediators generated by combination of .omega.-3 PUFA and aspirin)

IT Anti-inflammatory agents
Antiarthritics
(mechanism of inflammation treatment or prevention by .omega.-3 fatty acid and aspirin combination)

IT Fatty acids, biological studies
RL: BAC (Biological activity or effector, except adverse); BSU (Biological study, unclassified); THU (Therapeutic use); BIOL (Biological study); USES (Uses)
(polyunsatd., n-3; mechanism of inflammation treatment or prevention by .omega.-3 fatty acid and aspirin combination)

IT Drug delivery systems
(prodrugs; mechanism of inflammation treatment or prevention by

.omega.-3 fatty acid and aspirin combination)

IT 329900-75-6, cyclooxygenase 2
RL: BAC (Biological activity or effector, except adverse); BSU (Biological study, unclassified); BIOL (Biological study)
(aspirin-acetylated; lipid mediators generated by combination of .omega.-3 PUFA and aspirin)

IT 131339-23-6
RL: FMU (Formation, unclassified); FORM (Formation, nonpreparative)
(conversion of eicosapentaenoic acid by B. megaterium)

IT 50-78-2, Aspirin
RL: BAC (Biological activity or effector, except adverse); BSU (Biological study, unclassified); THU (Therapeutic use); BIOL (Biological study); USES (Uses)
(lipid mediators generated by combination of .omega.-3 PUFA and aspirin)

IT 60-33-3, Linoleic acid, biological studies 463-40-1, Linolenic acid 506-32-1, Arachidonic acid 29428-99-7, Dihomo-.gamma.-linoleic acid 71160-24-2, LTB4 80445-66-5, LTB5
RL: BPR (Biological process); BSU (Biological study, unclassified); BIOL (Biological study); PROC (Process)
(lipid mediators generated by combination of .omega.-3 PUFA and aspirin)

IT **6217-54-5**, Docosahexaenoic acid **10417-94-4**, Eicosapentaenoic acid
RL: BPR (Biological process); BSU (Biological study, unclassified); THU (Therapeutic use); BIOL (Biological study); PROC (Process); USES (Uses)
(lipid mediators generated by combination of .omega.-3 PUFA and aspirin)

IT 87042-40-8 88852-33-9 90780-51-1 90780-52-2 90780-53-3 90906-41-5 99217-78-4 141110-17-0 312516-13-5 356041-27-5
RL: FMU (Formation, unclassified); FORM (Formation, nonpreparative)
(lipid mediators generated by combination of .omega.-3 PUFA and aspirin)

IT 356041-12-8
RL: BPR (Biological process); BSU (Biological study, unclassified); BIOL (Biological study); PROC (Process)
(lipid mediators generated in inflammatory exudate by combination of .omega.-3 PUFA and aspirin)

IT 92008-51-0 312516-11-3 312516-12-4 312516-12-4D, isomers
RL: FMU (Formation, unclassified); FORM (Formation, nonpreparative)
(lipid mediators generated in inflammatory exudate by combination of .omega.-3 PUFA and aspirin)

IT 5598-33-4 13222-49-6 81370-31-2 356041-29-7
RL: FMU (Formation, unclassified); FORM (Formation, nonpreparative)
(products generated from dihomolinoleic acid and aspirin-acetylated COX-2)

IT **18104-45-5** 98524-19-7
RL: FMU (Formation, unclassified); FORM (Formation, nonpreparative)
(products generated from linoleic acid and aspirin-acetylated COX-2)

IT 36129-21-2 51197-09-2 81325-64-6 81325-65-7
RL: FMU (Formation, unclassified); FORM (Formation, nonpreparative)
(products generated from linolenic acid and aspirin-acetylated COX-2)

L10 ANSWER 3 OF 12 CAPLUS COPYRIGHT 2002 ACS
ACCESSION NUMBER: 2001:392686 CAPLUS
DOCUMENT NUMBER: 135:163888
TITLE: Binding of **13-HODE** and 15-HETE to phospholipid bilayers, albumin, and intracellular fatty acid binding proteins. Implications for transmembrane and intracellular transport and for protection from lipid peroxidation
AUTHOR(S): Mentzer, Bengt A. Ek-Von; Zhang, Fengli; Hamilton,

James A.
CORPORATE SOURCE: Departments of Preclinical Research and Development, Astrazeneca, Moelndal, 431 83, Swed.
SOURCE: Journal of Biological Chemistry (2001), 276(19), 15575-15580
CODEN: JBCHA3; ISSN: 0021-9258
PUBLISHER: American Society for Biochemistry and Molecular Biology
DOCUMENT TYPE: Journal
LANGUAGE: English
AB Transport and utilization of fatty acids (FA) in cells is a multistep process that includes adsorption to and movement across the plasma membrane and binding to intracellular fatty acid binding proteins (FABP) in the cytosol. We monitored the trans-bilayer movement of several polyunsatd. FA and oxidn. products (13-hydroxy octadecadienoic acid (HODE) and 15-hydroxytetraenoic acid (HETE)) in unilamellar protein-free phospholipid vesicles contg. a fluorescent pH probe. All FA diffused rapidly by the flip-flop mechanism across the model membrane, as revealed by pH changes inside the vesicle. This result suggests that FA oxidn. products generated in the cell could cross the plasma or nuclear membrane spontaneously without a membrane transporter. To illuminate features of extra- and intracellular transport, the partitioning of unsatd. FA and oxidized FA between phospholipid vesicles and albumin or FABP was studied by the pyranin assay. These expts. showed that all polyunsatd. FA and oxidized FA (**13-HODE** and 15-HETE) desorbed rapidly from the phospholipid bilayer to bind to bovine serum albumin, which showed a slight preference for the unsatd. FA over the oxidized FA. FABP rapidly bound FA in the presence of phospholipid bilayers, with a preference of **13-HODE** over the unsatd. FA and with a specificity depending on the type of FABP. Liver FABP was significantly more effective than intestinal FABP in binding **13-HODE** in the presence of vesicles. The more effective binding of the FA metabolite, **13-HODE**, than its precursor 18:2 by FABP may help protect cellular membranes from potential damage by monohydroxy fatty acids and may contribute a pathway for entry of **13-HODE** into the nucleus.
IT Proteins, specific or class
RL: BPR (Biological process); BSU (Biological study, unclassified); BIOL (Biological study); PROC (Process)
(FABP (fatty acid-binding protein), intestinal, liver; binding of **13-HODE** and 15-HETE to phospholipid bilayers, albumin, and intracellular fatty acid binding proteins)
IT Membrane, biological
(bilayer; binding of **13-HODE** and 15-HETE to phospholipid bilayers, albumin, and intracellular fatty acid binding proteins)
IT Molecular association
(binding of fatty acids to bovine serum albumin and fatty acid-binding protein)
IT Fatty acids, biological studies
RL: BPR (Biological process); BSU (Biological study, unclassified); BIOL (Biological study); PROC (Process)
(binding of fatty acids to bovine serum albumin and fatty acid-binding protein)
IT Albumins, biological studies
RL: BPR (Biological process); BSU (Biological study, unclassified); BIOL (Biological study); PROC (Process)
(serum, bovine; binding of **13-HODE** and 15-HETE to phospholipid bilayers, albumin, and intracellular fatty acid binding proteins)
IT Liposomes
(small unilamellar; binding of **13-HODE** and 15-HETE

to phospholipid bilayers, albumin, and intracellular fatty acid binding proteins)

IT 57-10-3, Palmitic acid, biological studies 60-33-3, Linoleic acid, biological studies 112-80-1, Oleic acid, biological studies 143-07-7, Lauric acid, biological studies 506-32-1, Arachidonic acid 5204-88-6, 9,11-Octadecadienoic acid, 13-hydroxy- **10417-94-4** 25448-00-4, Docosapentaenoic acid 71030-36-9, 15-HETE
RL: BPR (Biological process); BSU (Biological study, unclassified); BIOL (Biological study); PROC (Process)
(binding of **13-HODE** and 15-HETE to phospholipid bilayers, albumin, and intracellular fatty acid binding proteins)

REFERENCE COUNT: 38 THERE ARE 38 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L10 ANSWER 4 OF 12 CAPLUS COPYRIGHT 2002 ACS
ACCESSION NUMBER: 2000:702599 CAPLUS
DOCUMENT NUMBER: 133:362232
TITLE: Mechanism for the antitumor and anticachectic effects of n-3 fatty acids
AUTHOR(S): Sauer, Leonard A.; Dauchy, Robert T.; Blask, David E.
CORPORATE SOURCE: Bassett Research Institute, Cooperstown, NY, 13326, USA
SOURCE: Cancer Research (2000), 60(18), 5289-5295
CODEN: CNREA8; ISSN: 0008-5472
PUBLISHER: American Association for Cancer Research
DOCUMENT TYPE: Journal
LANGUAGE: English

AB The authors show that the addn. of .alpha.-linolenic acid or eicosapentaenoic acid (EPA)to arterial blood inhibits tumor fatty acid (FA) uptake, including linoleic acid (LA), and the subsequent conversion of LA to the mitogen 13-hydroxyoctadecadienoic acid (**13-HODE**) in vivo and during perfusion in situ. [3H]Thymidine incorporation during perfusion in situ was also inhibited. Addn. of **13-HODE** to the arterial blood reversed the inhibition of [3H]thymidine incorporation but had no effect on FA uptake. These two n-3 FAs also inhibited FA transport in inguinal fat pads in vivo and during perfusion in situ in fed (FA uptake) and fasted (FA release) rats. The effects of EPA and .alpha.-linolenic acid on transport of satd., monounsatd., and n-6 poly-unsatd. FAs in hepatoma 7288CTC and inguinal fat pads during perfusion in situ were reversed by the addn. of forskolin (1 .mu.M), pertussis toxin (0.5 .mu.g/mL), or 8-bromo-cAMP (10 .mu.M) to the arterial blood. The authors conclude that the antitumor and anticachectic effects of n-3 FAs on hepatoma 7288CTC and inguinal fat pads in vivo result from an inhibition of FA transport. These inhibitions are mediated by a putative n-3 FA receptor via a Gi protein-coupled signal transduction pathway that decreases intracellular cAMP. A specific decrease in LA uptake and its conversion to the mitogen **13-HODE** causes the tumor growth inhibition.

IT Antitumor agents
Biological transport
Cachexia
Nutrition, animal
(antitumor and anticachectic effects of n-3 fatty acids in relation to mechanism)

IT Liver, neoplasm
(hepatoma; antitumor and anticachectic effects of n-3 fatty acids in relation to mechanism)

IT Fatty acids, biological studies
RL: BAC (Biological activity or effector, except adverse); BPR (Biological process); BSU (Biological study, unclassified); BIOL (Biological study); PROC (Process)
(polyunsatd., omega-3; antitumor and anticachectic effects of n-3 fatty

acids in relation to mechanism)

IT Fatty acids, biological studies
RL: BOC (Biological occurrence); BPR (Biological process); BSU (Biological study, unclassified); BIOL (Biological study); OCCU (Occurrence); PROC (Process)
(uptake of; antitumor and anticachectic effects of n-3 fatty acids in relation to mechanism)

IT 29350-74-1
RL: ADV (Adverse effect, including toxicity); BSU (Biological study, unclassified); MFM (Metabolic formation); BIOL (Biological study); FORM (Formation, nonpreparative)
(antitumor and anticachectic effects of n-3 fatty acids in relation to mechanism)

IT **10417-94-4**, Eicosapentaenoic acid
RL: BAC (Biological activity or effector, except adverse); BPR (Biological process); BSU (Biological study, unclassified); BIOL (Biological study); PROC (Process)
(antitumor and anticachectic effects of n-3 fatty acids in relation to mechanism)

IT 463-40-1, .alpha.-Linolenic acid
RL: BAC (Biological activity or effector, except adverse); BSU (Biological study, unclassified); BIOL (Biological study)
(antitumor and anticachectic effects of n-3 fatty acids in relation to mechanism)

IT 60-33-3, Linoleic acid, biological studies
RL: BPR (Biological process); BSU (Biological study, unclassified); BIOL (Biological study); PROC (Process)
(uptake of; antitumor and anticachectic effects of n-3 fatty acids in relation to mechanism)

REFERENCE COUNT: 54 THERE ARE 54 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L10 ANSWER 5 OF 12 CAPLUS COPYRIGHT 2002 ACS

ACCESSION NUMBER: 2001:82583 CAPLUS
DOCUMENT NUMBER: 134:295096
TITLE: Anti-microinflammatory lipid signals generated from dietary n-3 fatty acids via cyclooxygenase-2 and transcellular processing: A novel mechanism for NSAID and n-3 PUFA therapeutic actions
AUTHOR(S): Serhan, Charles N.; Clish, C. B.; Brannon, J.; Colgan, S. P.; Gronert, K.; Chiang, N.
CORPORATE SOURCE: Center for Experimental Therapeutics and Reperfusion Injury, Department of Anesthesiology, Perioperative and Pain Medicine, Brigham and Women's Hospital and Harvard Medical School, Boston, MA, 02115, USA
SOURCE: Journal of Physiology and Pharmacology (2000), 51(4, Pt. 1), 643-654
CODEN: JPHPEI; ISSN: 0867-5910
PUBLISHER: Polish Physiological Society
DOCUMENT TYPE: Journal
LANGUAGE: English

AB Aspirin (ASA) inhibits prostaglandin (PG) biosynthesis and via acetylation of cyclooxygenase 2 (COX-2) it leads to bioactive lipoxins epimeric at carbon 15 (15-epi-LX, also termed aspirin-triggered lipoxins or ATL). Inflammatory exudates from mice treated with n-3 polyunsatd. fatty acids (PUFA) and ASA contain an array of bioactive lipids. Human endothelial cells, both HUVEC and microvascular, with upregulated COX-2 and treated with ASA convert C20:5n-3 to 18R-hydroxyeicosapentaenoic acid (HEPE) and 15R-HEPE. Human polymorphonuclear neutrophils (PMN) activated with serum-treated zymosan (STZ) utilize these R-HEPE compds. to produce trihydroxy mediators, including the 5-series 15R-LX and 5,12,18R-triHEPE. These novel products are potent inhibitors of human PMN transendothelial

migration and PMN infiltration into dorsal air pouches in vivo. In addn. to ASA, both acetaminophen and indomethacin also permit 18R-HEPE and 15R-HEPE generation with recombinant human COX-2 and n-5 and n-9 oxygenations of other fatty acids that act on leukocytes, blood platelets, and endothelial cells. These data establish new transcellular routes for producing arrays of lipid mediators via COX-2/nonsteroidal anti-inflammatory drugs (NSAID) and cell-cell interactions that impact microinflammation. They provide novel mechanism(s) that could underlie the many reported therapeutic benefits of n-3 dietary supplements of interest in inflammation, cancer, and vascular disorders.

IT Nutrition, animal
(dietary n-3 fatty acids and aspirin, acetaminophen and indomethacin effects on anti-microinflammatory prostaglandin metabolites produced by cyclooxygenase-2 and transcellular processing)

IT Prostaglandins
RL: BPR (Biological process); BSU (Biological study, unclassified); BIOL (Biological study); PROC (Process)
(dietary n-3 fatty acids and aspirin, acetaminophen and indomethacin effects on anti-microinflammatory prostaglandin metabolites produced by cyclooxygenase-2 and transcellular processing)

IT Fatty acids, biological studies
RL: FFD (Food or feed use); BIOL (Biological study); USES (Uses)
(polyunsatd., n-3; dietary n-3 fatty acids and aspirin, acetaminophen and indomethacin effects on anti-microinflammatory prostaglandin metabolites produced by cyclooxygenase-2 and transcellular processing)

IT 50-78-2, Aspirin 53-86-1, Indomethacin 103-90-2, Acetaminophen
RL: BAC (Biological activity or effector, except adverse); BSU (Biological study, unclassified); BIOL (Biological study)
(dietary n-3 fatty acids and aspirin, acetaminophen and indomethacin effects on anti-microinflammatory prostaglandin metabolites produced by cyclooxygenase-2 and transcellular processing)

IT 60-33-3, Linoleic acid, biological studies **10417-94-4** **18104-45-5, 13-Hode** 39391-18-9, Cyclooxygenase 73347-43-0, 11(R)-HETE 83603-31-0, 15(R)-HETE 95851-20-0 98524-19-7 104758-12-5 109430-11-7 312516-11-3 312516-12-4
RL: BPR (Biological process); BSU (Biological study, unclassified); BIOL (Biological study); PROC (Process)
(dietary n-3 fatty acids and aspirin, acetaminophen and indomethacin effects on anti-microinflammatory prostaglandin metabolites produced by cyclooxygenase-2 and transcellular processing)

REFERENCE COUNT: 35 THERE ARE 35 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L10 ANSWER 6 OF 12 CAPLUS COPYRIGHT 2002 ACS
ACCESSION NUMBER: 2000:379408 CAPLUS
DOCUMENT NUMBER: 133:102222
TITLE: Identification of 12-lipoxygenase products in the gills of carp, Cyprinus carpio
AUTHOR(S): Iijima, Noriaki; Chosa, Satoshi; Hada, Takahiko; Kayama, Mitsu
CORPORATE SOURCE: Faculty of Applied Biological Science, Hiroshima University, Hiroshima, 739-8528, Japan
SOURCE: Fisheries Science (2000), 66(2), 358-364
CODEN: FSCIEH; ISSN: 0919-9268
PUBLISHER: Japanese Society of Fisheries Science
DOCUMENT TYPE: Journal
LANGUAGE: English

AB A lipoxygenase was found in the crude enzyme soln. from the gills of carp, Cyprinus carpio. It oxidized arachidonic acid (AA) more efficiently than linoleic acid, eicosapentaenoic acid and docosahexaenoic acid. Lipoxygenase activity was constantly detected in the gill microsomes and

was found to be optimum at pH 7.2. It was not stimulated by reduced NADP and was not inhibited by SKF525A, a cytochrome P 450 inhibitor. The oxygenated products extd. from the reaction mixts. of crude enzyme soln. and AA were purified by reverse-phase and straight-phase HPLC. The major metabolite was identified as 12(S)-hydroxyeicosatetraenoic acid (12(S)-HETE) by UV spectrophotometry, gas chromatog.-mass spectrometry and chiral phase HPLC. In addn., 12-hydroxyeicosapentaenoic acid (12-HEPE) and 13-hydroxyoctadecadienoic acid (13-HODD) were also found in the reaction products as minor components. Similar results were obtained by the anal. of the reaction products of AA and carp gill microsomes. These results confirm the presence of 12-lipoxygenase in carp gill microsomes.

IT Carp (Cyprinus carpio)
Gill
Microsome
(lipoxygenase products in gills of carp Cyprinus carpio)

IT 82391-43-3, Oxygenase, arachidonate 12-lip-
RL: BOC (Biological occurrence); BPR (Biological process); BSU (Biological study, unclassified); BIOL (Biological study); OCCU (Occurrence); PROC (Process)
(lipoxygenase products in gills of carp Cyprinus carpio)

IT **18104-45-5** 54397-83-0 81187-21-5
RL: BSU (Biological study, unclassified); MFM (Metabolic formation); BIOL (Biological study); FORM (Formation, nonpreparative)
(lipoxygenase products in gills of carp Cyprinus carpio)

IT 60-33-3, Linoleic acid, reactions 506-32-1, Arachidonic acid **6217-54-5**, Docosahexaenoic acid **10417-94-4**, Eicosapentaenoic acid
RL: RCT (Reactant); RACT (Reactant or reagent)
(lipoxygenase products in gills of carp Cyprinus carpio)

REFERENCE COUNT: 38 THERE ARE 38 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L10 ANSWER 7 OF 12 CAPLUS COPYRIGHT 2002 ACS
ACCESSION NUMBER: 1998:43561 CAPLUS
DOCUMENT NUMBER: 128:165533
TITLE: Upregulation of nuclear PKC and MAP-kinase during hyperproliferation of guinea pig epidermis: modulation by 13-(S)-hydroxyoctadecadienoic acid (**13-HODE**)
AUTHOR(S): Mani, Indu; Iversen, Lars; Ziboh, Vincent A.
CORPORATE SOURCE: Department of Dermatology, University of California, Davis, CA, 95616, USA
SOURCE: Cellular Signalling (1998), 10(2), 143-149
CODEN: CESIEY; ISSN: 0898-6568
PUBLISHER: Elsevier Science Inc.
DOCUMENT TYPE: Journal
LANGUAGE: English

AB 13-(S)-Hydroxyoctadecadienoic acid (**13-HODE**), the lipoxygenase metabolite of linoleic acid, has been shown to reverse the epidermal hyperproliferation induced by topical application of docosahexaenoic acid (DHA, 22:6 n-3) on guinea pig skin. Our initial studies demonstrated that **13-HODE** exerts a selective inhibition of the membrane-bound PKC-.beta. activity in the hyperproliferative skin. To delineate the antiproliferative effects of **13-HODE**, we investigated the nuclear events assocd. with this process. Our data demonstrated that the major PKC isoenzymes in the epidermal nuclear fraction are .alpha. and .zeta.. Epidermal hyperproliferation induced by DHA caused an increase in nuclear total PKC and atypical PKC activities, and this was accompanied by an increase in the two nuclear isoenzymes, .alpha. and .zeta. ($P < 0.05$). This increase was reversed after topical application of **13-HODE**. Similarly, **13-HODE** suppressed elevated nuclear

MAP-kinase. Taken together, these data suggest that nuclear signalling events in the epidermis involve PKC-MAP-kinase pathway.

IT Skin
(epidermis, disease, hyperproliferation; upregulation of nuclear PKC and MAP-kinase during hyperproliferation of guinea pig epidermis, and its modulation by 13-(S)-hydroxyoctadecadienoic acid)

IT Skin, disease
(epidermis, hyperproliferation; upregulation of nuclear PKC and MAP-kinase during hyperproliferation of guinea pig epidermis, and its modulation by 13-(S)-hydroxyoctadecadienoic acid)

IT Skin
(epidermis; upregulation of nuclear PKC and MAP-kinase during hyperproliferation of guinea pig epidermis, and its modulation by 13-(S)-hydroxyoctadecadienoic acid)

IT Cell nucleus
(upregulation of nuclear PKC and MAP-kinase during hyperproliferation of guinea pig epidermis, and its modulation by 13-(S)-hydroxyoctadecadienoic acid)

IT **6217-54-5**, Docosahexaenoic acid **18104-45-5, 13-HODE**
RL: BAC (Biological activity or effector, except adverse); BSU (Biological study, unclassified); BIOL (Biological study)
(upregulation of nuclear PKC and MAP-kinase during hyperproliferation of guinea pig epidermis, and its modulation by 13-(S)-hydroxyoctadecadienoic acid)

IT 137632-07-6, p44 MAP kinase 137632-08-7, p42 MAP kinase 142805-58-1, MEK kinase
RL: BOC (Biological occurrence); BPR (Biological process); BSU (Biological study, unclassified); BIOL (Biological study); OCCU (Occurrence); PROC (Process)
(upregulation of nuclear PKC and MAP-kinase during hyperproliferation of guinea pig epidermis, and its modulation by 13-(S)-hydroxyoctadecadienoic acid)

IT 141436-78-4, Protein kinase C
RL: BAC (Biological activity or effector, except adverse); BOC (Biological occurrence); BSU (Biological study, unclassified); BIOL (Biological study); OCCU (Occurrence)
(.alpha. and .zeta. isoenzymes; upregulation of nuclear PKC and MAP-kinase during hyperproliferation of guinea pig epidermis, and its modulation by 13-(S)-hydroxyoctadecadienoic acid)

L10 ANSWER 8 OF 12 CAPLUS COPYRIGHT 2002 ACS
ACCESSION NUMBER: 1996:500475 CAPLUS
DOCUMENT NUMBER: 125:212853
TITLE: Dexamethasone induces bisallylic hydroxylation of polyunsaturated fatty acids by rat liver microsomes
AUTHOR(S): Hoernsten, Lena; Bylund, Johan; Oliw, Ernst H.
CORPORATE SOURCE: Div. Biochem. Pharmacol., Uppsala Univ. Biomed. Cent., Uppsala, S-751 24, Swed.
SOURCE: Archives of Biochemistry and Biophysics (1996), 332(2), 261-268
CODEN: ABBIA4; ISSN: 0003-9861
PUBLISHER: Academic
DOCUMENT TYPE: Journal
LANGUAGE: English

AB Human, monkey, and rat liver microsomes catalyze bisallylic hydroxylations of arachidonic and linoleic acids. The cytochrome P 450 gene family of these hydroxylases has not been detd. We examd. whether inducers of cytochrome P 450 could augment the bisallylic hydroxylation activity of male rat liver microsomes. The microsomes were incubated with [14C]linoleic acid and NADPH and the monohydroxy metabolites were characterized. Microsomes prepd. from control rats yielded mainly

18-hydroxyoctadecadienoic acid (18-HODE) and 17-HODE and microsomes from clofibrate-treated rats 18-HODE. Microsomes from .beta.-naphthoflavone-treated rats hydroxylated linoleic acid without position specificity, i.e., at carbons 8, 11, 14, 16, 17, and 18. 11-HODE, 17-HODE, and 18-HODE were major metabolites. Microsomes from rats treated with phenobarbital, isopropanol, imidazole, or acetone also formed these three products along with many other hydroxy metabolites. The synthetic glucocorticoid dexamethasone increased the biosynthesis of 11-HODE selectively. Microsomes from male Sprague-Dawley and Fischer rats treated with dexamethasone mainly formed 11-HODE and 18-HODE. The biosynthesis of 11-HODE was increased 10-fold and troleandomycin (50 .mu.M) inhibited the biosynthesis of 11-HODE by 90%. The bisallylic hydroxylases were also investigated with 14C-labeled arachidonic and eicosapentaenoic acids as substrates. Microsomes from rats treated with dexamethasone converted 20:4n-6 to 13-hydroxyeicosatetraenoic acid (13-HETE), 10-HETE, 7-HETE, 19-HETE, and 20-HETE. Induction by acetone yielded the same products. Microsomes from dexamethasone-treated rats metabolized 20:5n-3 to 16-hydroxyeicosapentaenoic acid (16-HEPE), 13-HEPE, 10-HEPE, 19-HEPE, and 20-HEPE as major products, while microsomes from control and acetone-treated rats mainly formed 19-HEPE and 20-HEPE. We conclude that microsomes from dexamethasone-treated rats catalyze bisallylic hydroxylations of 18:2n-6, 20:4n-6, and 20:5n-3, possibly by induction of bisallylic hydroxylases of the CYP3A subfamily.

IT Liver
Microsome
(dexamethasone induces polyunsatd. fatty acid bisallylic hydroxylation in rat liver microsomes)

IT Corticosteroids, biological studies
RL: BAC (Biological activity or effector, except adverse); BSU (Biological study, unclassified); BIOL (Biological study)
(gluco-, dexamethasone induces polyunsatd. fatty acid bisallylic hydroxylation in rat liver microsomes)

IT Fatty acids, biological studies
RL: BPR (Biological process); BSU (Biological study, unclassified); BIOL (Biological study); PROC (Process)
(polyunsatd., dexamethasone induces polyunsatd. fatty acid bisallylic hydroxylation in rat liver microsomes)

IT 50-02-2, Dexamethasone
RL: BAC (Biological activity or effector, except adverse); BSU (Biological study, unclassified); BIOL (Biological study)
(dexamethasone induces polyunsatd. fatty acid bisallylic hydroxylation in rat liver microsomes)

IT 60-33-3, Linoleic acid, biological studies 506-32-1, Arachidonic acid 9035-51-2, Cytochrome P 450, biological studies **10417-94-4**
RL: BPR (Biological process); BSU (Biological study, unclassified); BIOL (Biological study); PROC (Process)
(dexamethasone induces polyunsatd. fatty acid bisallylic hydroxylation in rat liver microsomes)

IT 4546-58-1, 17-Hydroxyoctadeca-9Z,12Z-dienoic acid 4546-59-2, 18-Hydroxyoctadeca-9Z,12Z-dienoic acid **18104-45-5, 13-HODE** 79551-85-2, 19-Hydroxyeicosa-5Z,8Z,11Z,14Z-tetraenoic acid 79551-86-3, 20-Hydroxyeicosa-5Z,8Z,11Z,14Z-tetraenoic acid 116477-57-7, 20-Hydroxyeicosa-5Z,8Z,11Z,14Z,17Z-pentaenoic acid 116477-58-8, 19-Hydroxyeicosa-5Z,8Z,11Z,14Z,17Z-pentaenoic acid 143288-68-0 180968-85-8 180968-86-9 180968-87-0 181141-17-3 181227-45-2
RL: BSU (Biological study, unclassified); MFM (Metabolic formation); BIOL (Biological study); FORM (Formation, nonpreparative)
(dexamethasone induces polyunsatd. fatty acid bisallylic hydroxylation in rat liver microsomes)

L10 ANSWER 9 OF 12 CAPLUS COPYRIGHT 2002 ACS
ACCESSION NUMBER: 1991:59520 CAPLUS

DOCUMENT NUMBER: 114:59520
TITLE: Formation of 15-lipoxygenase product from docosahexaenoic acid (22:6w3) by human platelets
AUTHOR(S): Kim, H. Y.; Karanian, J. W.; Salem, N., Jr.
CORPORATE SOURCE: Sect. Anal. Chem., NIAAA, Bethesda, MD, 20892, USA
SOURCE: Prostaglandins (1990), 40(5), 539-49
CODEN: PRGLBA; ISSN: 0090-6980
DOCUMENT TYPE: Journal
LANGUAGE: English

AB The metab. of docosahexaenoic acid (22:6w3) by 15-lipoxygenase activity of washed human platelets was investigated. Platelets produced 17-hydroxydocosahexaenoic acid when incubated with 22:6w3. Similarly, 15-hydroxyeicosatetraenoic acid and 13- and 9-hydroxyoctadecadienoic acids (HODD) were produced when incubated with 20:4w6 and 18:2w6, resp. However, these products were obsd. only as minor components in the platelet incubation mixt. Control studies with carefully purified platelets and mononuclear cells indicated that these products were formed by the platelets. Chiral phase HPLC anal. indicated that these compds. were mainly in the S configuration with the exception of the 9-HODD, thus, confirming that a lipoxygenase is responsible for their prodn. The 9-HODD produced by platelets was a racemic mixt.

IT Blood platelet
(docosahexaenoic acid metab. by, of human, lipoxygenase in)

IT Fatty acids, biological studies
RL: BPR (Biological process); BIOL (Biological study); PROC (Process)
(polyunsatd., n-6, metab. of, by blood platelet of human)

IT 82249-77-2, 15-Lipoxygenase
RL: BIOL (Biological study)
(docosahexaenoic acid metab. by, of blood platelet of human)

IT **18104-45-5** 73180-00-4, 15-Hydroxyeicosatetraenoic acid
RL: FORM (Formation, nonpreparative)
(formation of, from arachidonic or linoleic acids by blood platelet of human)

IT 92693-03-3
RL: FORM (Formation, nonpreparative)
(formation of, from docosahexaenoic acid by blood platelet of human)

IT 98524-19-7
RL: FORM (Formation, nonpreparative)
(formation of, from linoleic acid by blood platelet of human)

IT 60-33-3, Linoleic acid, biological studies 506-32-1, Arachidonic acid
RL: BPR (Biological process); BIOL (Biological study); PROC (Process)
(metab. of, by blood platelet of human)

IT **6217-54-5**, Docosahexaenoic acid
RL: BPR (Biological process); BIOL (Biological study); PROC (Process)
(metab. of, by blood platelet of human, lipoxygenase in)

L10 ANSWER 10 OF 12 CAPLUS COPYRIGHT 2002 ACS
ACCESSION NUMBER: 1990:197018 CAPLUS
DOCUMENT NUMBER: 112:197018
TITLE: Induction of epidermal hyperproliferation by topical n-3 polyunsaturated fatty acids on guinea pig skin linked to decreased levels of 13-hydroxyoctadecadienoic acid (**13-HODE**)
AUTHOR(S): Miller, Craig C.; Ziboh, Vincent A.
CORPORATE SOURCE: Sch. Med., Univ. California, Davis, CA, 95616, USA
SOURCE: J. Invest. Dermatol. (1990), 94(3), 353-8
CODEN: JIDEAE; ISSN: 0022-202X
DOCUMENT TYPE: Journal
LANGUAGE: English

AB Reversal of essential fatty acid deficiency (EFA)-induced epidermal hyperproliferation was recently suggested to require linoleic acid and an

active lipoxygenase product. Because the nature of this lipoxygenase product is unknown, a model of n-3 polyunsatd. fatty acid (PUFA)-induced hyperproliferation in guinea pig skin was employed to test a possible reversal of the hyperproliferation by an oxidative metabolite of linoleic acid. Topical applications of two n-3 PUFA, 0.5% of eicosapentaenoic acid (20:5n-3) and(or) of docosahexaenoic acid (22:6n-3) for 5 days induced severe epidermal hyperproliferation. Development of the epidermal hyperproliferation paralleled a marked decrease in the major epidermal linoleic acid lipoxygenase product, **13-HODE**. The application of 0.1% of **13-HODE** to the n-3 PUFA-induced guinea pig hyperproliferative skin resulted in the restoration of normal epidermal histol. and reversal of hyperproliferation as detd. by epidermal uptake of 3H-thymidine. These data support the view that **13-HODE** may represent the endogenous cutaneous mediator necessary for full restoration of cutaneous symptoms of essential fatty acid deficiency. Furthermore, the topical use of n-3 PUFA for the disruption of normal metab. of skin n-6 EFA (linoleic acid) does serve as a useful tool for further investigations into the regulatory mechanisms of in vivo epidermal proliferation/differentiation.

IT Phospholipids, biological studies
RL: BIOL (Biological study)
(fatty acids of, of skin epidermis, topical application of .omega.-3 fatty acids effect on, epidermal hyperproliferation in relation to)

IT Deoxyribonucleic acid formation
(in skin epidermis, topical application of .omega.-3 fatty acids effect on, epidermal hyperproliferation in relation to)

IT Fatty acids, biological studies
RL: BIOL (Biological study)
(of neutral lipids and phospholipids, of skin epidermis, .omega.-3 fatty acid topical application effect on, epidermal hyperproliferation in relation to)

IT Skin, disease or disorder
(epidermis, hyperproliferation, from .omega.-3 polyunsatd. fatty acid topical application, hydroxyoctadecadienoic acid formation in relation to)

IT Fatty acids, biological studies
RL: FORM (Formation, nonpreparative)
(hydroxy, formation of, in skin epidermis, topical application of .omega.-3 fatty acids effect on, epidermal hyperproliferation in relation to)

IT Lipids, biological studies
RL: BIOL (Biological study)
(neutral, fatty acids of, of skin epidermis, topical application of .omega.-3 fatty acids effect on, epidermal hyperproliferation in relation to)

IT Fatty acids, biological studies
RL: BIOL (Biological study)
(polyunsatd., n-3, epidermal hyperproliferation response to topical application of, hydroxyoctadecadienoic acid formation in relation to)

IT 54845-95-3, 15-HETE
RL: FORM (Formation, nonpreparative)
(formation of, in skin epidermis, topical application of .omega.-3 fatty acids effect on, epidermal hyperproliferation in relation to)

IT **18104-45-5**
RL: FORM (Formation, nonpreparative)
(formation of, in skin epidermis, topical application of .omega.-3 polyunsatd. fatty acids effect on, hyperproliferation in relation to)

IT 112-80-1, 9-Octadecenoic acid (Z)-, biological studies 557-59-5, Tetracosanoic acid
RL: BIOL (Biological study)
(of neutral lipids and phospholipids, of skin epidermis, .omega.-3 fatty acid topical application effect on, epidermal hyperproliferation

in relation to)

IT **6217-54-5**, Docosahexaenoic acid **10417-94-4**, Eicosapentaenoic acid
RL: BIOL (Biological study)
(skin epidermis hyperproliferation response to topical application of, hydroxyoctadecadienoic acid formation in relation to)

L10 ANSWER 11 OF 12 CAPLUS COPYRIGHT 2002 ACS
ACCESSION NUMBER: 1990:117061 CAPLUS
DOCUMENT NUMBER: 112:117061
TITLE: Guinea pig epidermis generates putative anti-inflammatory metabolites from fish oil polyunsaturated fatty acids
AUTHOR(S): Miller, Craig C.; Yamaguchi, Ronald Y.; Ziboh, Vicent A.
CORPORATE SOURCE: Sch. Med., Univ. California, Davis, CA, 95616, USA
SOURCE: Lipids (1989), 24(12), 998-1003
CODEN: LPDSAP; ISSN: 0024-4201
DOCUMENT TYPE: Journal
LANGUAGE: English

AB Clin. studies have indicated that dietary fish oil may have therapeutic value in the treatment of psoriasis, a hyperproliferative, inflammatory skin disorder characterized by elevated LTB4. To evolve a possible mechanism for these beneficial effects, the metabolic fate of fish oil-derived n-3 fatty acids was detd. in the skin. Specifically, guinea pig epidermal enzyme prepns. were incubated with [3H]eicosapentaenoic acid (20:5n-3) and [14C]docosahexaenoic acid (22:6n-3). Analyses of the radiometabolites revealed the transformation of these n-3 fatty acids into n-6 lipoxygenase (arachidonate 15-lipoxygenase) products: 15-hydroxyeicosapentaenoic acid (15-HEPE) and 17-hydroxydocosahexaenoic acid (17-HDHE), resp. Since 15-lipoxygenase products have been suggested to be possible endogenous inhibitors of 5-lipoxygenase (an enzyme which catalyzes the formation of LTB4), the ability of 15-HEPE and 17-HDHE in vitro to inhibit the activity of the 5-lipoxygenase was tested. Incubations of these metabolites with enzyme prepns. from rat basophilic leukemia (RBL-1) cells demonstrated that 15-HEPE (50% inhibitory concn. (IC50) = 28 .mu.M) and 17-HDHE (IC50 = 25 .mu.M) are potent inhibitors of the RBL-1 5-lipoxygenase. The inhibitory potential of these fish oil metabolites provides a possible mechanism by which fish oil might act to decrease local cutaneous levels of LTB4, and thereby alleviate psoriatic symptoms.

IT Psoriasis
(therapy of, anti-inflammatory metabolite formation from polyunsatd. fatty acids of fish oil in epidermis in relation to)

IT Skin, metabolism
(epidermis, anti-inflammatory metabolite formation from polyunsatd. fatty acids of fish oil in, psoriasis therapy in relation to)

IT Oils, glyceridic
RL: BIOL (Biological study)
(fish, in psoriasis therapy, anti-inflammatory metabolite formation from polyunsatd. fatty acids in skin epidermis in relation to)

IT Fatty acids, biological studies
RL: BIOL (Biological study)
(polyunsatd., n-3, of fish oil, anti-inflammatory metabolite formation from, in skin epidermis, psoriasis therapy in relation to)

IT 80619-02-9, 5-Lipoxygenase
RL: BIOL (Biological study)
(fish oil polyunsatd. fatty acid metabolites inhibition of, in skin epidermis, psoriasis therapy in relation to)

IT **18104-45-5** 54845-95-3 70608-72-9 88852-33-9 90780-52-2
RL: FORM (Formation, nonpreparative)
(formation of, from polyunsatd. fatty acids of fish oil in skin

epidermis, LTB4 formation inhibition and psoriasis therapy in relation to)

IT 71160-24-2, Leukotriene B4
RL: FORM (Formation, nonpreparative)
(formation of, in skin epidermis, polyunsatd. fatty acids of fish oil effect on, psoriasis therapy in relation to)

IT **6217-54-5**, Docosahexaenoic acid **10417-94-4**, Eicosapentaenoic acid
RL: BPR (Biological process); BIOL (Biological study); PROC (Process)
(metab. of, by skin epidermis, fish oil therapy for psoriasis in relation to)

IT 82249-77-2, Arachidonate 15-lipoxygenase
RL: BIOL (Biological study)
(polyunsatd. fatty acids of fish oil metab. by, in skin epidermis, LTB4 formation inhibition and psoriasis therapy in relation to)

L10 ANSWER 12 OF 12 CAPLUS COPYRIGHT 2002 ACS

ACCESSION NUMBER: 1985:200071 CAPLUS
DOCUMENT NUMBER: 102:200071
TITLE: Characterization and separation of the arachidonic acid 5-lipoxygenase and linoleic acid .omega.-6 lipoxygenase (arachidonic acid 15-lipoxygenase) of human polymorphonuclear leukocytes
AUTHOR(S): Soberman, Roy J.; Harper, Timothy W.; Betteridge, David; Lewis, Robert A.; Austen, K. Frank
CORPORATE SOURCE: Dep. Med., Harvard Med. Sch., Boston, MA, 02115, USA
SOURCE: J. Biol. Chem. (1985), 260(7), 4508-15
CODEN: JBCHA3; ISSN: 0021-9258
DOCUMENT TYPE: Journal
LANGUAGE: English

AB The cytosolic fraction of human polymorphonuclear leukocytes pptd. with 60% (NH4)2SO4 produced 5-lipoxygenase (I) products from [14C]arachidonic acid and .omega.-6 lipoxygenase products from both [14C]linoleic acid and, to a lesser extent, [14C]- and [3H]arachidonic acid. The I products 5-hydroperoxy-6,8,11,14-eicosatetraenoic acid (5-HPETE) and 5-hydroxy-6,8,11,14-eicosatetraenoic acid (5-HETE) derived from [14C]arachidonic acid, and the .omega.-6 lipoxygenase products 13-hydroperoxy-9,11-octadecadienoic acid (13-OOH linoleic acid) and 13-hydroxy-9,11-octadecadienoic acid (13-OH linoleic acid) derived from [14C]linoleic acid and 15-hydroperoxy-5,8,11,13-eicosatetraenoic acid (15-HPETE), and 15-hydroxy-5,8,11,13-eicosatetraenoic acid (15-HETE) derived from [14C]- and [3H]arachidonic acid were identified by TLC-autoradiog. and by reverse-phase HPLC. I had a pH optimum of 7.5 and was 50% maximally active at a Ca2+ concn. of 0.05 mM; the Km for prodn. of 5-HPETE/5-HETE from arachidonic acid was 12.2 .mu.M, and the Vmax was 2.8 nmol/min/mg protein. The .omega.-6 linoleic lipoxygenase had a pH optimum of 6.5 and was 50% maximally active at a Ca2+ concn. of 0.1 mM in the presence of 5 mM EGTA. When I and the .omega.-6 lipoxygenase were sepd. by DEAE-Sephadex ion exchange chromatog., the .omega.-6 lipoxygenase exhibited a Km of 77.2 .mu.M and a Vmax of 9.5 nmol/min/mg protein for conversion of linoleic acid to 13-OOH/13-OH linoleic acid and a Km of 63.1 .mu.M and a Vmax of 5.3 nmol/min/mg protein for formation of 15-HPETE/15-HETE from arachidonic acid.

IT Michaelis constant
(of arachidonic acid 5-lipoxygenase and linoleic acid .omega.-6 lipoxygenase, of human polymorphonuclear leukocytes)

IT Kinetics, enzymic
(of inhibition, of linoleic acid .omega.-6 lipoxygenase of human polymorphonuclear leukocytes)

IT Cytoplasm
(cytosol, arachidonic acid 5-lipoxygenase and linoleic acid .omega.-6 lipoxygenase of, of human polymorphonuclear leukocytes)

IT Leukocyte
(polymorphonuclear, arachidonic acid 5-lipoxygenase and linoleic acid .omega.-6 lipoxygenase of cytosol of, of human)
IT 7440-70-2, biological studies
RL: BIOL (Biological study)
(arachidonic acid 5-lipoxygenase and linoleic acid .omega.-6 lipoxygenase requirement for, in human polymorphonuclear leukocytes)
IT 67675-14-3 69371-38-6
RL: FORM (Formation, nonpreparative)
(formation of, from arachidonic acid by arachidonic acid 15-lipoxygenase of human polymorphonuclear leukocytes)
IT 70968-82-0 71030-39-2
RL: FORM (Formation, nonpreparative)
(formation of, from arachidonic acid by arachidonic acid 5-lipoxygenase of human polymorphonuclear leukocytes)
IT **18104-45-5** 23017-93-8
RL: FORM (Formation, nonpreparative)
(formation of, from linoleic acid by linoleic acid .omega.-6 lipoxygenase of human polymorphonuclear leukocytes)
IT 82249-77-2
RL: BIOL (Biological study)
(linoleic acid .omega.-6 lipoxygenase with activity of, of human polymorphonuclear leukocytes, sepn. and characterization of)
IT 9029-60-1 80619-02-9 82249-77-2
RL: BIOL (Biological study)
(of polymorphonuclear leukocytes, of human, sepn. and properties of)
IT 506-32-1
RL: RCT (Reactant)
(reaction of, with arachidonic acid 5-lipoxygenase and linoleic acid .omega.-6 lipoxygenase of human polymorphonuclear leukocytes, kinetics of)
IT **10417-94-4**
RL: RCT (Reactant)
(reaction of, with arachidonic acid 5-lipoxygenase of human polymorphonuclear leukocytes, kinetics of)
IT 60-33-3, reactions
RL: RCT (Reactant)
(reaction of, with linoleic acid .omega.-6 lipoxygenase of human polymorphonuclear leukocytes, kinetics of)

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Asia Pacific J Clin Nutr (1995) 4: 314-318

The relationship between linoleic acid level in serum, adipose tissue and myocardium in humans

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A cross-sectional study of 80 consecutive cases at necropsy was undertaken to determine the relationship between linoleic acid in the serum, adipose tissue and myocardium of humans. The sample consisted of 55 males and 25 females aged 7 to 92 years who had died from cardiac and non-cardiac causes in the Southern Region of Tasmania, Australia. Fatty acids were extracted from samples of serum, adipose tissue and myocardium and separated using capillary gas liquid chromatography. Means and standard deviations were calculated for each of the main fatty acids in the three tissues studied. In serum and adipose tissue, there were significantly higher levels of linoleic acid ($p<0.001$ and $p<0.001$ in serum and adipose tissue, respectively) and total n-6 fatty acids ($p< 0.002$ and $p< 0.001$ in serum and adipose tissue, respectively) and significantly lower levels of oleic acid in females than in males ($p< 0.001$ and $p<0.05$ in serum and adipose tissue, respectively). In serum and adipose tissue, the ratio of total n-6 to total n-3 fatty acids was significantly higher in females than males ($p<0.02$ and $p<0.001$ in serum and adipose tissue, respectively). In myocardium, there were significantly higher levels of oleic acid ($p<0.05$) and linoleic acid ($p<0.001$) and significantly lower levels of arachidonic acid ($p<0.001$) and docosapentaenoic acid ($p<0.02$) in females than males. Total n-3 fatty acids in myocardium were significantly lower in females ($p<0.001$) resulting in a significantly higher ratio of total n-6 to total n-3 fatty acids in females ($p<0.001$). Highly significant Pearson correlations were found between levels of linoleic acid in adipose tissue and myocardium ($p<0.0001$), between adipose tissue and serum ($p<0.001$) and between serum and myocardium ($p<0.001$). The proportion of total polyunsaturated fatty acids (PUFA) in the myocardium was inversely related to the proportion of monounsaturated fatty acids ($p<0.001$) and inversely related to the proportion of saturated fatty acids ($p<0.001$). There was a significant positive correlation between the ratio of linoleic acid to linolenic acid in all three tissues. This study showed that there was a very strong relationship between the level of linoleic acid in adipose tissue and myocardial tissue, which suggests that dietary linoleic acid influences the level of myocardial linoleic acid. These findings support the hypothesis that dietary linoleic acid has a direct influence on myocardial membrane linoleic acid levels.

Intr duction

Analysis of population trends in dietary consumption suggests an inverse relationship between dietary levels of PUFA and mortality from CHD[1]. The finding, that the fatty acid content of subcutaneous fat is a good biological indicator of fat consumption in humans[2,3], has resulted in a number of epidemiological studies using adipose tissue samples to confirm the inverse relationship between dietary levels of PUFA (in particular linoleic acid) and the risk of mortality from CHD[4,5,6]. A recent study has shown an inverse relationship between levels of linoleic acid in adipose tissue and the risk of sudden cardiac death[7]. These findings in humans are supported by results of animal studies which suggest a direct effect of dietary fatty acid levels on phospholipid fatty acid composition[8]. Such changes in the fatty acid composition of myocardial phospholipid can influence the susceptibility of the

myocardium to develop arrhythmias, and may account for the association between dietary fatty acids and sudden cardiac death[9].

Given the association between dietary fat, adipose tissue, fatty acid composition and the risk of sudden cardiac death, it is important to establish whether dietary linoleic acid, as reflected in levels of linoleic acid in adipose tissue, correlates significantly with linoleic acid levels in human myocardium. The aim of this study was to examine the correlation between levels of linoleic acid in serum, adipose tissue and myocardium from humans.

Methods

Tissue samples

Where possible, samples of serum (n=62), adipose tissue (n=79) and myocardium (n=79) were taken at necropsy from 80 consecutive cases. The cases included 55 males and 25 females who died from cardiac and non cardiac causes. Ages ranged from 7 years to 92 years. Ethical approval for the collection of tissue samples was granted by the Ethics Committee of the Royal Hobart Hospital.

Serum samples were obtained from blood aspirated from cardiac chambers, usually the left ventricle. Adipose tissue was sampled from the anterior abdominal wall and myocardium was sampled from areas of macroscopically normal myocardium, that is, myocardium free of fibrosis and not involved in a recent myocardial infarction.

Specimens were placed into plastic containers and stored at -70° C until analysis.

Analysis of tissue fatty acids

Lipids were extracted from the thawed samples in chloroform-methanol (2:1) as described previously[10]. Aliquots of the total lipids, together with an internal standard of heptadecanoic acid, were treated with KOH in methanol followed by BF3 in methanol.[10] The resulting fatty acid methyl esters were separated by capillary gas liquid chromatography using a 50mm x 0.32mm (ID) CP Sil 88 column (Chrompack, Middelburgh, The Netherlands). The column oven was operated from 110° C to 190° C using helium as the carrier gas at a linear gas velocity of 20 cm/sec. Standard fatty acid methyl esters were routinely chromatographed to establish retention times and to determine response factors for the individual fatty acid methyl esters.

Statistical methods

Means and standard deviations were calculated for each of the main fatty acids in the three tissues studied. Comparisons of mean levels of fatty acids in the tissues studied were calculated using the Students t-test. Correlations were calculated using the Pearson correlation coefficient (r). Correlations did not vary by sex or cause of death and therefore total sample results are given.

Results

The fatty acid composition of the three tissues in males and females is shown in the Table. The main fatty acids in serum were palmitic acid (16:0), palmitoleic acid (16:1), stearic acid (18:0), oleic acid (18:1), linoleic acid (18:2n-6), arachidonic acid (20:4n-6) and docosahexaenoic acid (22:6n-3). In serum, there were significantly higher levels of linoleic acid ($p<0.001$) and total n-6 PUFA ($p<0.002$) and significantly lower levels of oleic acid in females than in males ($p<0.001$). The ratio of total n-6 to total n-3 PUFA was significantly higher in females ($p<0.02$).

Table. Serum, adipose tissue and myocardial fatty acid composition in males and females

		Males			Females		
		Serum n=39	Adipose n=54	Myocardium n=54	Serum n=23	Adipose n=25	Myocardium n=25
Fatty Acid		Mean± SD[a]	Mean± SD	Mean± SD	Mean± SD[a]	Mean± SD	Mean± SD
Saturated							
Myristic	14:0	1.06± 0.41	3.10± 0.99	1.09± 0.50	1.25± 0.77	2.91± 0.88	1.17± 0.66
Palmitic	16:09	21.78± 2.48	22.19± 2.17	16.33± 1.77	22.12± 3.50	22.25± 2.50	16.74± 2.45
Stearic	18:09	7.31± 1.39	5.57± 1.59	11.61± 1.56	7.37± 1.17	5.30± 1.74	11.33± 1.77
Monounsaturated							
Palmitoleic	16:1	2.87± 1.17	5.88± 1.89	1.75± 0.86	2.70± 1.57	5.35± 2.30	1.93± 1.31
Oleic	18:1[b]	25.72± 3.75[f]	45.84± 5.72[c]	21.22± 6.42	23.03± 4.15	44.38± 7.43	22.54± 6.78[c]
Eicosamonoenoic	20:1	0.66± 0.20	1.34± 0.31	0.67± 0.62	0.60± 0.13	1.33± 0.21	0.56± 0.23
Polyunsaturated							
Linoleic	18:2n-6	25.40± 6.83	10.18± 4.16	16.76± 3.72	28.14± 7.37[f]	12.26± 3.67[f]	18.60± 3.94[f]
Linolenic	18:3n-3	0.45± 0.19	0.38± 0.08	0.25± 0.14	0.33± 0.10	0.36± 0.10	0.23± 0.11
Eicosadienoic	20:2n-6	0.17± 0.07	0.14± 0.06	0.14± 0.09	0.16± 0.07	0.16± 0.04	0.15± 0.04
Eicosatrienoic	20:3n-6	1.27± 0.56	0.15± 0.07	0.81± 1.48	1.24± 0.42	0.20± 0.10	0.58± 0.18
Arachidonic	20:4n-6	6.79± 1.67	0.44± 0.33	15.75± 4.58[f]	6.55± 1.62	0.37± 0.15	13.93± 3.67
Eicosapentaenoic	20:5n-3	0.73± 0.42	0.07± 0.18	0.55± 0.40	0.60± 0.38	0.01± 0.04	0.33± 0.16
Docosatetraenoic	22:4n-6	0.21± 0.08	0.09± 0.07	0.33± 0.16	0.17± 0.08	0.13± 0.11	0.30± 0.09
Docosapentaenoic	22:5n-6	0.12± 0.18	0.02± 0.04	0.25± 0.14	0.09± 0.08	0.00± 0.01	0.16± 0.11
	22:5n-3	0.62± 0.19	0.23± 0.12	1.47± 0.49[d]	0.51± 0.19	0.27± 0.17	1.08± 0.40
Docosahexaenoic	22:6n-3	1.78± 0.60	0.26± 0.42	3.29± 1.00	1.96± 1.09	0.21± 0.19	2.82± 1.32
	n-6	33.96± 7.06	11.01± 4.22	34.05± 6.04	36.35± 8.61[e]	13.13± 3.62[f]	33.79± 7.18
	n-3	3.58± 1.03	0.94± 0.61	5.56± 1.45[f]	3.41± 1.45	0.85± 0.40	4.46± 1.68
	n-6/n-3	10.58± 4.39	15.55± 10.95	6.50± 1.73	11.96± 4.52[d]	18.61± 9.07[d]	9.28± 7.30[f]

a results shown as mean ± SD of g fatty acid per 100g total fatty acids. **b** 18:1n-7 and 18:1n-9. **c** $p<0.05$ **d** $p<0.02$ **e** $p<0.002$ **f** $p<0.001$ Position of superscripts **c, d, e, f** indicate gender with significantly higher level of tissue fatty acid. **g** 16 and 18-carbon aldehydes determined as dimethyl acetal derivatives (DMA) were found in myocardium at levels of 3.25± 1.19 and 3.04± 1.09 for 16:0 DMA for males and females respectively, and 1.48± 0.82 and 1.37± 0.75 for 18:0 DMA for males and females respectively.

The main fatty acids in adipose tissue were myristic acid (14:0), palmitic acid, palmitoleic acid, stearic acid, oleic acid and **linoleic** acid. In adipose tissue, there were significantly higher levels of **linoleic** acid ($p<0.001$) and total n-6 PUFA ($p<0.001$) and significantly lower levels of oleic acid ($p<0.05$) in females than males. The ratio of total n-6 to total n-3 PUFA in adipose tissue was significantly higher in females than in males ($p<0.001$).

The main fatty acids in myocardium were palmitic acid, stearic acid, oleic acid, **linoleic** acid, arachidonic acid and docosahexaenoic acid. Fatty aldehydes were also detected in this tissue and the levels are reported in the Table. In myocardium, there were significantly higher levels of oleic acid ($p<0.05$) and **linoleic** acid ($p<0.001$) and significantly lower levels of arachidonic acid ($p<0.001$) and docosapentaenoic acid (22:5n-3) ($p<0.002$) in females than males. Total n-3 fatty acids were significantly lower in females ($p<0.001$) resulting in a significantly higher ratio of total n-6 to total n-3 fatty acids in females ($p<0.001$).

Figures 1 to 3 show that there were highly significant correlations between levels of **linoleic** acid in adipose tissue and myocardium ($p<0.0001$), between adipose tissue and serum ($p<0.001$) and between serum and myocardium ($p<0.001$).

Figure 1. Correlation between levels of **linoleic** acid (18:2n-6) in adipose tissue and myocardium (as a percentage of total fatty acids in adipose tissue and myocardium).

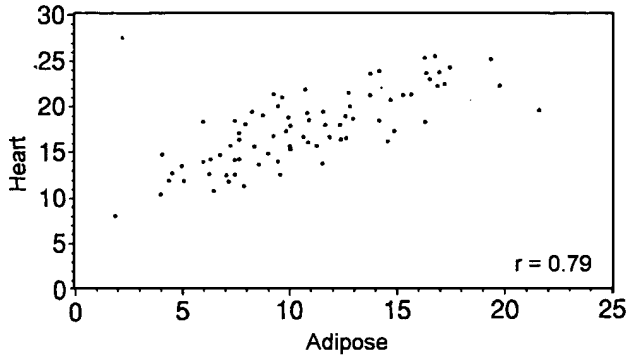


Figure 2. Correlation between levels of linoleic acid (18:2n-6) in serum and adipose tissue (as a percentage of total fatty acids in serum and adipose tissue).

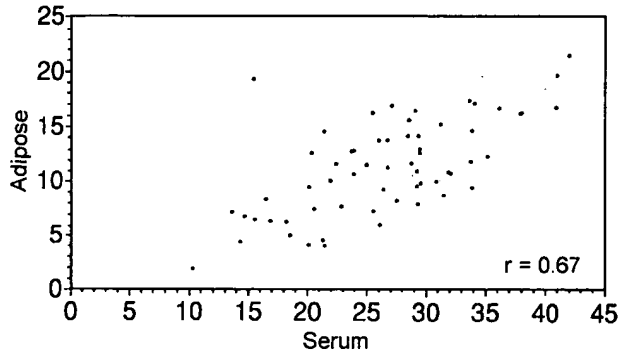
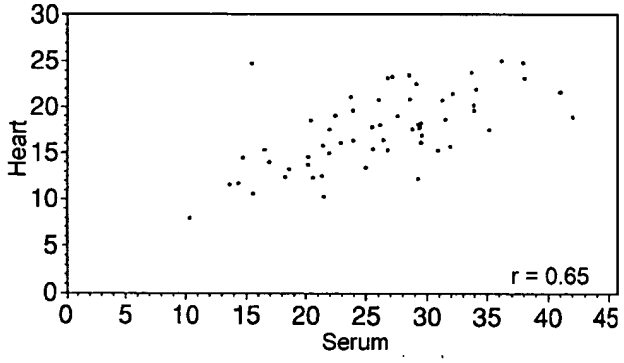


Figure 3. Correlation between levels of linoleic acid (18:2n-6) in serum and myocardium (as a percentage of total fatty acids in serum and myocardium).



Discussion

This study showed a very strong relationship between the level of linoleic acid in adipose tissue and myocardial tissue, which suggests that dietary linoleic acid influences the level of myocardial linoleic acid.

Previous studies have shown that adipose linoleic acid levels reflected dietary linoleic acid intake.[2,3] The transport of linoleic acid from the gut via chylomicrons and subsequent transport in various lipoprotein classes derived from the liver would ensure that all tissues would be likely to incorporate essential PUFA via the action of lipoprotein lipases. Thus, it was not surprising that we showed a strong relationship between the level of linoleic acid in heart and adipose tissue. These findings support the hypothesis that dietary PUFA can have a direct influence on myocardial membrane PUFA. The beneficial effects of linoleic acid might be derived by the displacement of saturated fatty acids in the myocardium as suggested by Riemersma[11]. In this study, we found that the proportion of PUFA (all n-6 and n-3 PUFA) in the myocardium was inversely related to the proportion of monounsaturated fatty acids ($r=0.962$, $p<0.001$). In particular, there was an inverse relationship between oleic acid (the main monounsaturated fatty acid) and arachidonic acid ($r=0.872$, $p<0.001$), and between oleic acid and linoleic acid ($r=0.530$,

p<0.001). It was also found that the proportion of PUFA was inversely correlated with the proportion of saturated fatty acids (r=0.491, p<0.001). Thus, increased PUFA levels in the myocardium were mainly associated with a reduced level of monounsaturated fatty acids but also with a reduction in saturated fatty acids.

The presence of linoleic acid itself may be beneficial by acting as a precursor of specific substances in the myocardium such as 13-hydroxyoctadecadienoic acid[12], or as a result of conversion to arachidonic acid, it may stimulate production of myocardial eicosanoids[13]. There was a positive relationship between the level of linoleic acid and arachidonic acid in the myocardium (r=0.253, p<0.05).

The level of saturated fatty acids and polyunsaturated fatty acids in adipose tissue in the present study fell between those reported by Riemersma et al, for three northern European countries and Italy.[4] That is, the levels of saturated fatty acids were lower and those for linoleic acid were higher than the northern European countries.

There is an increasing interest in dietary n-3 PUFA in relation to processes involved in atherosclerosis, thrombosis and cardiac arrhythmias. It has been suggested that eicosapentaenoic acid (20:5n-3) reduces the production of a variety of eicosanoids derived from arachidonic acid, leading to a reduced production of pro-inflammatory, pro-aggregatory and pro-arrhythmogenic eicosanoids such as thromboxane and the 4-series leukotrienes[13,14]. Therefore, we investigated whether there was a relationship between the main n-6 and n-3 PUFA in the three tissues.

Since there is competition between linoleic acid and linolenic acid for metabolism to longer chain PUFA such as arachidonic acid and eicosapentaenoic acid in the liver, diets with high levels of linoleic acid relative to linolenic acid result in tissue with high levels of n-6 PUFA relative to n-3 PUFA[15] and presumably high levels of eicosanoids derived from arachidonic acid[14].

In this study, there was a significant positive correlation between the ratio of linoleic acid to linolenic acid in all three tissues (myocardium v adipose, r=0.23, p<0.05, n=79; myocardium v serum, r=0.19, p<0.05, n=62; adipose v serum, r=0.44, p<0.001, n=62). Since others have shown that the relationship between diet and adipose tissue PUFA is correlated[2,3], these data support the concept of a positive relationship between the ratio of linoleic acid to linolenic acid in the diet and myocardial tissue. The ratio of linoleic acid to linolenic acid in adipose tissue was also significantly correlated with the ratio of total n-6 PUFA to total n-3 PUFA in myocardial tissue (r=0.42, p<0.001, n=79). Since myocardial tissue lipids contain high levels of 20 and 22-carbon PUFA derivatives of linoleic acid and linolenic acid, this correlation suggests that the ratio of dietary n-6 PUFA to n-3 PUFA influences the proportion of these two PUFA families in myocardial tissue.

Female subjects had significantly elevated levels of linoleic acid in all three tissues compared with males. This could be due to differences in dietary intake, however data from the 1990 Victorian Nutrition Survey of about 3,000 randomly selected subjects did not reveal any difference in PUFA intake (as percentage of energy) between males and females[16]. Another reason for the difference could be genetic and this is supported by several studies which have reported higher levels of linoleic acid in female subjects in plasma phospholipids[17], heart tissue phospholipids[18] and adipose tissue[19].

This study showed that there was a very strong relationship between the level of linoleic acid in adipose tissue and myocardial tissue, which suggests that dietary linoleic acid influences the level of myocardial linoleic acid. These findings support the hypothesis that dietary linoleic acid can have a direct influence on myocardial membrane linoleic acid. These findings might account for the beneficial effects of linoleic acid in reducing sudden cardiac death[7].

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The relationship between linoleic acid level in serum, adipose tissue and myocardium in humans

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亞油酸水平在人血清、脂肪組織和心肌間的關係

摘要

作者進行了 80 個連續屍體解剖，以測定亞油酸在人血清、脂肪組織和心肌之間的關係。研究對象在澳大利亞塔斯曼尼亞省（Tasmania）南區收集，包括 55 位男性和 25 位女性，年齡在 7 - 92 歲，對象是死於心臟病和非心臟病的患者。從血清、脂肪組織和心肌抽提脂肪酸，並用氣相層析法分離。計算三種組織主要脂肪酸的平均數和標準差。結果發現，血清和脂肪組織中亞油酸含量明顯增高（分別爲 $p < 0.001$ 和 $p < 0.001$），同時 N-6 脂肪酸總量也明顯增高（分別爲 $p < 0.002$ 和 $p < 0.001$）。另一方面，女性的油酸含量明顯低於男性（分別爲 $p < 0.001$ 和 $p < 0.05$）。女性血清和脂肪組織中的 N-6 脂肪酸和 N-3 脂肪酸比值明顯高於男性（分別爲 $p < 0.02$ 和 $p < 0.001$）。女性心肌中的油酸和亞油酸明顯高於男性（分別爲 $p < 0.05$ 和 $p < 0.001$），但廿碳四烯酸和廿二碳五烯酸則明顯低於男性（分別爲 $p < 0.001$ 和 $p < 0.002$）。女性心肌的 N-3 脂肪酸總量明顯下降（$p < 0.001$），結果使總 N-6 脂肪酸和 N-3 脂肪酸的比值明顯升高（$p < 0.001$）。作者還發現脂肪組織和心肌中亞油酸含量有明顯的 Pearson 相關（$p < 0.0001$），脂肪組織和血清間的相關爲 $p < 0.001$，血清和心肌之間的相關爲 $p < 0.001$。多不飽和脂肪酸（PUFA）在心肌中的總含量與單不飽和脂肪酸與飽和脂肪酸的含量呈負相關（分別爲 $p < 0.001$ 和 $p < 0.001$）。三種組織中的亞油酸與亞麻酸的比值呈明顯正常關。該研究顯示亞油酸在脂肪組織和心肌的含量有十分明顯的關係，指出了膳食亞油酸含量影響心肌亞油酸水平。該研究支持膳食亞油酸會直接影響心肌膜亞油酸含量的假說。

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Editors note:

Not all studies support the notion that the levels of tissue **linoleic** acid currently achieved by some individuals in industrialised, affluent societies are cardio-protective, at least insofar as coronary artery disease is concerned[20,21]. The present paper does not, of course, consider health outcome in relation to tissue fatty acid status.

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REVIEW: Natural Eicosanoids in Regulation of Blood Coagulation

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Metabolites of polyunsaturated fatty acids, primarily arachidonic **acid**, are important physiological regulators of blood coagulation. In contrast to many other substances involved in coagulation, eicosanoids affect virtually all links of hemostasis; they are responsible for blood vessel wall thromboresistance and its acquisition of procoagulant properties in response to various agonists, regulate the extent of cell-to-cell interactions, modulate reactions of plasma hemostasis and blood fibrinolytic activity, and change hemodynamic parameters. Such complex effects of eicosanoids on thrombogenesis suggest that they are unique and extremely important biologically active substances that strongly determine the balance of anticoagulant and procoagulant factors.

KEY WORDS: polyunsaturated fatty acids, arachidonic **acid**, oxylipins, eicosanoids, blood coagulation system

Abbreviations: AA) arachidonic **acid**; GP) glycoprotein; HETE) hydroxyeicosatetraenoic acids; 13-HODE) **13-hydroxyoctadecadienoic acid**; HPETE) hydroperoxyeicosatetraenoic acids; IL) interleukin; LT) leukotriene; NO) nitric oxide; PG) prostaglandin; PGI_2) prostacyclin; PUFA) polyunsaturated fatty acids; TNF) tumor necrosis factor; TXA_2) thromboxane A_2.

In the whole body free of any pathological factors, the liquid state of the blood is maintained

by an equilibrium of factors that facilitate and counteract coagulation. The blood coagulation potential is maintained within physiological limits by a complex mechanism involving many factors of peptide and other natures and maintaining certain physical and physicochemical constants that determine the intensity of interactions between separate components of the blood coagulation system. In this situation, polyunsaturated fatty acids and products of their metabolism perform unique functions. These substances are involved in regulation of virtually all links of homeostasis, through both direct effects on components of this process and indirect effects through coupled physiological systems. Polyunsaturated fatty acids are structural and functional components of absolutely all tissues and their metabolites are essential factors of cellular activities [1]; therefore, full characterization of pathways of influences of these biologically active substances on the blood coagulation system is virtually impossible. Another aspect of effects of endogenous oxylipins is their involvement in pathogenic reactions that are the basis for various diseases. We think that reviewing this function of metabolites of polyunsaturated fatty acids is a separate task requiring thorough analysis of pathogeneses of each disease, which is beyond the scope of this review. Therefore, we found it expedient to consider only the most important (and probably the least extensively studied) aspects of interactions of certain natural oxylipins on blood coagulation in the absence of systemic diseases that could cause prothrombogenic changes (atherosclerosis, diabetes, malignant tumors, etc.). Before reviewing data available from the literature, it should be noted that no direct evidence exists for the presence of physiologically significant amounts of certain endogenous oxylipins *in vivo* at the site of thrombus formation [2]. Although *in vitro* studies and *in vivo* evaluation of their effects as exogenous substances showed that these substances are involved in thrombogenesis, their significance for regulation of hemostasis is difficult to determine [3].

Among all derivatives of polyunsaturated fatty acids (PUFA), metabolites of arachidonic **acid** play the most important role in normal functioning of hemostasis in mammals. The main fraction of arachidonic **acid** in cells is bound to membrane phospholipids. The level of free arachidonic **acid** (AA) is very low and is one of the most important factors determining the rate of generation of eicosanoids [4]. Two pathways provide the necessary levels of AA for the synthesis of blood oxylipins. First, AA can be released from membrane phospholipids by phospholipase A_2. Second, plasma low-density lipoproteins can be sources of AA [5]. After liberation of AA from reserves, its metabolism follows several enzymatic pathways. Metabolites produced by all enzymatic processes are involved in regulation of hemostasis.

As pointed out above, metabolites of PUFA, AA metabolites in particular, are involved in regulation of virtually all links of the blood coagulation system. These metabolites facilitate the manifestations of thromboresistant and procoagulant properties of vascular walls, modulate the interactions between cells of the same type (aggregation) and different types (adhesion), interfere with processes of plasma hemostasis, change the blood fibrinolytic potential, and affect hemodynamic conditions. It should be noted, however, that cells involved in hemostasis are probably the main targets of thrombomodulatory effects of oxylipins, whereas all other effects are mainly of a secondary nature and can be explained by effects of PUFA metabolites on metabolic processes in particular cells.

Undamaged endotheliocytes that form the vessel lining are thromboresistant [6]. What causes the thromboresistance of intact vascular walls remains largely unclear; however, PUFA metabolites are certainly necessary components of this complex physiological system [7]. Most authors suggest that intact endothelial cells cannot synthesize and release

prostacyclin (PGI_2) or other oxylipins [8-10], although a rapid but short-term increase in the level of PGI_2 occurs in response to various agonists, such as thrombin, AA, and trypsin, that increase the level of intracellular calcium ions [11, 12]. Induction of PGI_2 synthesis requires a relatively high level of intracellular free calcium, which should be higher than that required for initiation of NO formation [12, 13]. However, physiological values of shear stress *in vivo* are probably sufficient for obtaining a level of cytoplasmic Ca^{2+} that would stimulate endothelial cells to produce and release factors, including prostacyclin, that impart thromboresistant properties to vascular walls [14, 15].

Among PUFA metabolites, PGI_2 is not the only factor of thromboresistance of vascular walls. The release of AA from membrane phospholipids is known to occur only upon stimulation of cells by agonists. Lipoxygenase remains active even in resting cells; however, in this case its main substrate is linoleic **acid** derived from cell triglycerides. **Triglyceride** metabolism is a permanent process in intact neutrophils, tumor cells, macrophages, fibroblasts, epithelial cells, platelets, endotheliocytes, smooth muscle cells, and some other cell types [16-18]; in these processes, triglycerides liberate linoleic **acid**, which in endotheliocytes is metabolized by 15-lipoxygenase to **13-hydroxyoctadecadienoic acid** (13-HODE).

Stimulation of endotheliocytes with thrombin, endotoxin, interleukin-1 (IL-1), and certain other cytokines, rapidly decreases the synthesis of 13-HODE. In contrast, increases in the level of intracellular cAMP activate the formation of 13-HODE [17], and natural metabolites that increase the intracellular cAMP level, such as PGI_2 and 6-keto-PGE_1, can initiate the metabolism of triglycerides in endothelial cells after a transitory inhibition of this process caused by damage of vascular wall thromboresistance, e.g., of traumatic origin [19]. The amount of 13-HODE in intact endothelial cells was shown to inversely correlate with the degree of thrombogenicity of endotheliocyte plasma membranes [2, 20]. Studies of the mechanism of anti-adhesive effects of 13-HODE showed that this metabolite regulates the expression of adhesion receptors (primarily vitronectin receptors) on the surface of endothelial cells. 13-HODE and vitronectin receptors are known to have the same cellular localization; they are found in vesicles placed directly under the plasma membrane. In intact endotheliocytes, 13-HODE interacts with lipophilic sites of vitronectin receptors, thereby decreasing their expression on the plasma membrane [2]. In stimulated endothelial cells, complexes of 13-HODE and vitronectin receptors dissociate with expression of active integrins on the apical surface of endotheliocytes; this increases their ability to interact with platelets and other circulating blood cells. An interesting finding was that 13-HODE is expressed not only on the apical surface of endotheliocytes but also on their basal surface, thereby maintaining the thromboresistance of subendothelial structures [2, 20, 21]. Such a localization of 13-HODE is an important factor modulating thrombogenesis, because the maximum activity of tissue factor expressed by stimulated vascular walls (one of the main components determining the extent of thrombogenesis possible under given conditions) is known to be related exactly to the basal surface of endothelial cells [22-24].

Most probably, metabolites of *gamma*-linolenic **acid** (18:3, *n*-6) are involved in maintenance of thromboresistant properties of cell walls. At least, there is evidence that adding black currant **oil**, which contains high levels of linoleic and *gamma*-linolenic acids, to rabbit diet causes a much greater increase in 13-HODE synthesis in comparison to nut **oil** that contains linoleic **acid** only [21]. This is probably related to an increase in the rate of synthesis of

dihomo-*gamma*-linolenic acid and then PGE_1 from *gamma*-linolenic acid; PGE_1 promotes the accumulation of cAMP in endotheliocytes, thereby activating linoleic acid metabolism and synthesis of 13-HODE [25]. Functional or morphological damage to vascular wall changes the thromboresistant properties of its luminal surface to procoagulant properties; this process can initiate thrombogenesis [6]. Depending on the nature of the damaging factor, these changes can be transitory or display properties of a chronic process [13]. In the former case, initial stimulation of endotheliocytes is mainly mediated by thrombin. Chronic disorders in vascular wall thromboresistance can be caused by certain factors such as endotoxin and pro-inflammatory cytokines, especially IL-1 and tumor necrosis factor; in this case, there is a considerable suppression of anticoagulant mechanisms, including the inhibition of prostacyclin synthesis [13, 26].

Upon interaction of thrombin with specific receptors on endotheliocytes, the cells synthesize, express, and liberate into the environment a range of biologically active substances causing procoagulant and anticoagulant effects. When applied to endotheliocytes, thrombin primarily causes a rapid increase in the rate of synthesis and secretion of strong anti-aggregants (PGI_2 and NO) capable of limiting the development of intravascular coagulation. Soon after application of weak stimuli to endothelial cells, there is an increase in the release of endothelial relaxing factor (NO) only, whereas liberation of PGI_2 requires much stronger stimuli, probably because of different pathways of transduction of signals inducing the synthesis of these mediators [12]. Such a sequence of liberation of NO and PGI_2 can be explained by biological expediency because NO is sufficient to block probable prothrombogenic reactions to weak stimulation of endothelium. This is also related to the fact that the initial stage of thrombogenesis is accompanied by active adhesion of cells to the surface of the vascular wall, making the synthesis of NO the most expedient response because this substance displays not only anti-aggregatory but also strong anti-adhesive effects [27-29]. After the formation of a monolayer of deposited platelets, their further accumulation mainly obeys the laws of platelet--platelet interaction (aggregation). This explains a short time delay in PGI_2 synthesis; this substance is one of the most potent natural anti-aggregatory agents; it can potentiate both the anti-aggregatory and disaggregatory effects of NO [27], but its physiological concentrations do not modulate adhesion to an appreciable extent [30] because the anti-adhesive effect develops only in the presence of high concentrations of PGI_2 causing an increase in intracellular cGMP level [27, 31].

Activation of endotheliocytes causes the formation of not only AA metabolites of the cyclooxygenase pathway, but also its metabolites of the lipoxygenase pathway, which also can modulate blood coagulation. Hydroxyeicosatetraenoic acids (HETEs) were shown to increase the rate of PGI_2 synthesis [32] thereby inhibiting thrombogenesis. However, HETEs can compete with arachidonic acid for lipoxygenase, cyclooxygenase, or both enzymes [33, 34], thereby inducing disorders in normal metabolism of PUFA. In this context, the observed decrease in the synthesis of PGI_2 by endothelial cells exposed to HETEs [35] is most probably a result of exhaustion of cyclooxygenase in the presence of excess substrate [2]. 15-Hydroperoxyeicosatetraenoic acid (15-HPETE) and 15-HETE can also decrease the procoagulatory activity of endotheliocytes stimulated by tumor necrosis factor *alpha* (TNF-*alpha*); this effect is mediated by neither a decrease in TNF-*alpha* binding to specific cell receptors nor a decrease in expression and/or synthesis of the tissue factor [36].

The loss of thromboresistance of endotheliocytes is accompanied by activation of blood coagulation. All blood cells are involved in thrombogenesis; however, the procoagulant function is the main function of platelets. Platelets are not only the main cell type involved in thrombogenesis in arteries and important factors of phlebothrombosis, but also strongly affect other links of blood coagulation: they supply activated phospholipid surfaces necessary for plasma hemostasis [37, 38], release certain blood coagulation factors in the blood [39], modulate fibrinolysis [40], and alter hemodynamic constants by causing a transitory vasoconstriction induced by their release of thromboxane A_2 (TXA_2) [41] and producing and releasing mitogens that induce hyperplasia of vascular walls [42]. Initiation of thrombogenesis is accompanied by activation of platelets and induction of their adhesion, release reaction, and aggregation; adhesion is the first step of hemostasis, which precedes the release reaction and aggregation [43, 44]. Platelet activation caused by vascular wall lesions, rheological disorders, etc., is due to interaction of surface receptors of these cells with certain agonists [45, 46]. Collagen and thrombin [47] are primary inducers appearing most frequently at the site of a vascular lesion; however, the complete formation of a platelet thrombus requires many other molecules as well. It should be noted that activated platelets display much higher affinities for ligands [47, 48]. Thus, glycoprotein (GP) IIb/IIIa of intact platelets can interact only with immobilized fibrinogen [49], whereas GPIIb/IIIa receptors of activated platelets display affinities for at least four different molecules: fibrinogen, von Willebrand's factor, fibronectin, and vitronectin [50].

Interactions of platelet receptors with specific ligands initiates a range of biochemical responses including the activation of G-proteins and phospholipases, phospholipid turnover, formation of second messengers, protein phosphorylation, metabolism of AA, interactions of actin and myosin, Na^+/H^+ exchange, expression of fibrinogen receptors, and redistribution of Ca^{2+} [51-55]. An obligatory stage of platelet activation is liberation of arachidonic **acid** with subsequent formation of TXA_2 [56], which stimulates the liberation of AA from platelet membrane phospholipids, thereby maintaining the cell activation [57]. However, TXA_2 alone cannot maintain platelet--platelet interactions because the initiation of platelet aggregation requires stimulation of receptors capable of inducing responses related to phospholipases A_2 and C [53].

In addition to TXA_2, other metabolites of AA are involved in platelet adhesion and aggregation. Platelets are known to produce more 12-HETE than TXA_2 [2]. 12-HPETE and 12-HETE can probably produce synergistic responses or are necessary for platelets to display their functional properties [20, 58, 59]. 12-HPETE, a precursor of 12-HETE, was found to potentiate platelet aggregation induced by arachidonic **acid** by inducing disorders in membrane permeability, thereby making more arachidonic **acid** available to cells [58]. In addition, selective inhibition of the 12-lipoxygenase pathway in platelets is known to decrease their adhesive ability independently of the effect of this treatment on platelet aggregation [60]. Adhesion of platelets to thrombogenic surfaces is accompanied by spreading the cells over the surface. This ensures better interactions of platelet GPIIb/IIIa receptors with fixed ligands and promotes thrombogenesis because this provides a stronger attachment of adherent cells with vascular walls and allows immobilized fibrinogen and von Willebrand's factor to act as platelet agonists that activate these cells [43]. Oxylipins are strongly involved in regulation of platelet spreading. Arachidonic **acid** liberated from activated cells is metabolized by lipoxygenase, and biologically active substances generated in this process initiate the production of diacylglycerol, which activates phospholipase C

required for the cell spreading [61]. Functioning of platelets probably involves epoxyeicosatrienoic acids and 20-HETE (arachidonic **acid** metabolites synthesized in reactions involving cytochrome P-450), which are liberated from membrane phospholipids upon platelet stimulation [62].

In response to stimulation by agonists, platelets also liberate certain stable prostaglandins (PG) having two double bonds, such as PGE_2, PGF_{2alpha}, and PGD_2. PGD_2 can inhibit platelet aggregation [63], PGF_{2alpha} activates these cells [64], and the effects of PGE_2 on platelets can vary [65] depending on whether adenylate cyclase is activated or inhibited by this substance [66]. We cannot exclude the possibility that all these compounds are involved in thrombogenesis [67]. Mechanisms of action of these eicosanoids are mediated by receptors found on platelet membranes [45].

In addition to stable prostaglandins, mainly PGE_2 and small amounts of thromboxane A_2, vascular walls produce prostacyclin, which is the main metabolite of the cyclooxygenase pathway in this tissue. PGI_2 is known to be produced in endothelial cells from not only endogenous labile peroxides, but also from exogenous, platelet-derived PGG_2 and PGH_2 [68]. In addition, PGI_2 can be synthesized in whole blood in the absence of endothelial cells [69]; this synthesis probably occurs in leukocytes and/or monocytes [70]. Prostacyclin is one of the most potent natural anti-aggregatory substances [71]. PGI_2 can increase the level of intracellular cAMP by activating adenylate cyclase; this suppresses the primary and secondary phases of platelet aggregation, suppresses the mobilization of intracellular Ca^{2+}, and inhibits the procoagulant activity of platelets [72].

Probably, not only PGI_2 proper but also its metabolic products are involved in regulation of thrombogenesis. PGI_2 is converted to certain stable but inactive products, mainly PGF_{1alpha}. It was suggested that endothelial cells can produce 6-keto-PGE_1, an active metabolite of PGI_2 [2]. This prostanoid has an anti-aggregatory effect comparable to that of PGI_2 but causes no appreciable hypotensive effect [73]. In the absence of any stimuli, 6-keto-PGE_1 is probably not synthesized by vascular walls (the only exception may be heart endotheliocytes), and production of its physiologically significant amounts occurs only upon cell--cell interactions [2]. The production of 6-keto-PGE_1 is probably a transcellular process. However, it should be noted that certain authors regard 6-keto-PGE_1 detection *in vitro* and *in vivo* as an artefact due to methodological flaws [74].

Among natural oxylipins, not only prostacyclin causes a strong inhibitory effect on platelet functions. PGE_1 synthesized in cells from dihomo-*gamma*-linolenic **acid** is a very important substance involved in regulation of blood coagulation. PGE_1 inhibits platelet aggregation [75, 76], increases the level of intracellular cAMP, inhibits the activation of protein kinase C and myosin light chain kinase in platelets stimulated by thrombin, and suppress their phosphatidylinositol-4,5-bisphosphate hydrolysis [76, 77] thereby preventing platelet activation through pathways dependent on and independent of AA metabolites of the cyclooxygenase pathway.

The functional balance between antithrombogenic and prothrombogenic reactions can be

disturbed by interference of not only activated platelets but also other blood cells subjected to appropriate stimulation. For example, interactions between erythrocytes and activated platelets increase their reaction abilities [78]. In addition, erythrocytes, like other blood cells, promote the synthesis of thrombin [79]. Leukocytes are another cell type involved in blood coagulation and fibrinolysis. They provide, upon stimulation, an active surface for initiation of hemostasis [80] and liberate substances that facilitate the involvement of other cells in blood coagulation and stimulate these cells [37, 81, 82]. Under certain conditions, leukocytes express endotoxin, which can increase vascular permeability independently of cell adhesion [83]; it also causes liberation of tissue factor and promotes the initiation of blood coagulation in the intrinsic pathway [37]. Activated monocytes secrete a range of cytokines, including IL-1*alpha* and IL-1*beta*, tumor necrosis factor, and probably IL-6 [84]; these can induce reactions of the blood coagulation cascade [13, 85].

Adhesion of white blood cells to vascular walls caused by low-density lipoprotein oxidation products, bacterial lipopolysaccharides, cytokines, and other agonists [86] has certain consequences important not only for the development of inflammatory reactions but also for an increase in the risk of thrombogenesis. This process causes disorders in interactions between separate endotheliocytes [87] which can increase vascular wall permeability and facilitate the access of procoagulant factors to subendothelial structures, thereby considerably increasing the probability of blood coagulation under certain conditions. In addition, adherent leukocytes can increase the prothrombogenic activity of vascular walls, probably through potentiation of production of a platelet aggregation factor by endothelial cells [88], liberating cytokines from activated cells, and/or a directly activating effect on endotheliocytes caused by adherent leukocytes [89]. All these processes lead to an increase in expression of tissue factor by endothelial cells. White blood cells are also involved in regulation of fibrinolysis. They activate $alpha_2$-antiplasmin, an important inhibitor of plasmin [90] and facilitate the utilization of soluble fibrin complexes [91]; on the other hand, they synthesize cytokines that suppress fibrinolysis by decreasing the liberation of tissue plasminogen activator from endotheliocytes and increasing the level of tissue plasminogen inhibitor [13].

A very important effect of activated leukocytes is their ability to produce and liberate mitogens that cause vascular wall proliferation [92] (which can lead to a disorder of synthesis and interaction of endothelial anticoagulation factors [93]), change hemodynamic constants, and induce acute thromboses.

These data suggest that erythrocytes and white blood cells are strongly involved in reactions of the blood coagulation cascade; therefore, modulation of their functions by metabolites of polyunsaturated fatty acids is important for maintaining a physiological balance between procoagulant and anticoagulant links of the blood coagulation system.

Studies of eicosanoids as substances affecting the functional activity of erythrocytes showed that PGI_2 increases the fluidity of these cells [94], thereby preventing probable rheological disorders and stasis. Lipoxygenase metabolites 15-HPETE, 15-HETE, and 12-HETE produce dose-dependent potentiation of adhesion of platelets to endothelial cells of large blood vessels and capillaries; the effects of 12-HETE are mediated by vitronectin receptors [95].

Studies of the effects of eicosanoids on white blood cells showed that PGI_2 considerably

suppresses the procoagulant activity of monocytes, which prevents, to some extent, the induction of certain blood coagulation reactions [96]. The thrombogenicity of monocytes can be decreased by other oxylipins, especially 5-, 12-, and 15-HETE [97]. However, other authors showed that platelet 12-HETE, a lipoxygenase metabolite of arachidonic acid, stimulates the procoagulant activity of monocytes and promotes the expression of tissue factor on the surface of these cells [98]. AA metabolites are also involved in regulation of production of cytokines. The rate of production of TNF-*alpha* and IL-1 by monocytes is determined by the rate ratio of generation of PGE_2 and TXA_2 by these cells; the latter substance increases the ability of nonadherent monocytes to synthesize cytokines [99]. Prostacyclin, another prostanoid, inhibits the liberation of cytokines, primarily tumor necrosis factor and IL-1, from monocytes and macrophages [100].

Interactions of platelets and polymorphonuclear neutrophils at the sites of a vascular lesions can promote thrombogenesis [101, 102]. Adhesion of these cells to each other provokes transcellular exchange of mediators and intermediate metabolites. This process requires the expression of P-selectin, which is responsible for "recognition" of platelets by polymorphonuclear neutrophils [103] on the platelet surface. However, a decrease in platelet reactivity decreases the expression of these surface receptors and this prevents the activation of the coagulation cascade as a result of platelet--leukocyte interactions. On the other hand, initiation of the intrinsic pathway of blood coagulation by leukocytes is accompanied by the formation of 5-lipoxygenase metabolites of arachidonic acid (leukotriene B_4 (LTB_4) and cysteine-containing leukotrienes) in human peripheral monocytes in a process largely independent of thrombin production [104]. This can result in creation of conditions for further promotion of coagulation. Certain studies showed that LTB_4 mediates the liberation of lysosomal enzymes from leukocytes, mobilization of calcium, and the formation of reactive oxygen species [105]. LTB_4, which is involved in pathophysiological processes of inflammation [106], causes adhesion of neutrophils to vascular walls followed by diapedesis and cell migration to the extracellular space [107]. This suggests that LTB_4 plays an anti-inflammatory role and can be involved in reactions leading to suppression of thromboresistance of endotheliocytes [88]. Lipoxin A_4, another arachidonic acid metabolite of the lipoxygenase pathway, can inhibit certain effects of LTB_4. In particular, lipoxin A can inhibit leukocyte migration and increase in vascular permeability induced by LTB_4 [108], thereby preventing the development of disorders caused by blood coagulation and inflammation.

Oxylipins can also produce secondary effects on plasma hemostasis, mainly through modulation of the procoagulant properties of cytoplasmic membranes. As pointed out above, activation of many cells involved in hemostasis is accompanied by expression of tissue factor on their surface. When the level of tissue factor increases to a certain value, it imparts thrombogenic properties to vascular walls [109] or other surfaces involved. The tissue factor (thromboplastin) is a transmembrane protein, which possesses no enzymatic activity but acts as a cofactor of the activated factor VII. The complex of tissue factor--factor VII can activate factors X and IX, which ultimately results in generation of thrombin [110]. Thrombin produced in this process is a key enzyme mediating the transformation of fibrinogen into fibrin and causing an additional activation of platelets [111]. Therefore, thrombin induces cell-mediated hemostasis and facilitates plasma-mediated reactions by strongly increasing the procoagulant properties of membranes of activated cells [112]. In

addition to this mechanism, thrombin can also increase the probability of platelet involvement in blood coagulation by increasing their expression of surface receptors for TXA_2/PGH_2 [113]. In this process, prostacyclin, which increases the level of cyclic nucleotides in endothelial cells, is involved in regulation of processes that facilitate the inactivation of thrombin found in the vascular lumen. At high levels of cAMP in endotheliocytes, the expression of thrombomodulin, which acts as a receptor of activated thrombin, increases on the luminal surface of the intima. Thrombin bound to thrombomodulin undergoes conformational changes that prevent its involvement in fibrin formation but make it highly active in reactions of cleavage of protein C zymogen, thereby facilitating its anticoagulatory effect [114].

Prostacyclin causes considerable activating effects on the blood fibrinolytic potential. PGI_2, which stimulates fibrinolysis *in vivo*, causes no profibrinolytic effect *in vitro* upon its direct application on fibrin plates [115]. An increase in fibrinolytic activity caused by PGI_2 administration can be caused by induction of liberation of tissue plasminogen activator from vascular walls [116]. A certain role in PGI_2-mediated modulation of the blood fibrinolytic potential can be played by its ability to inhibit platelet functions. Platelets are known to be strongly involved in regulation of thrombolysis. First of all, they are an important source of tissue plasminogen activator and $alpha_2$-antiplasmin [117]. When exposed to agonists, platelets can liberate these substances from intracellular organelles, thereby suppressing fibrinolysis [40]. However, platelets accumulate endogenous prourokinase on their surface [118], a phenomenon whose physiological significance is still unknown [118], and platelet-associated prourokinase can activate plasminogen at the site of thrombogenesis [37, 119]. Plasmin generated simultaneously can cause a direct stimulatory effect on platelets [120] and thus increased the risk of thrombosis. These data indicate that the profibrinolytic effect of platelets is of less significance than their antifibrinolytic effects. Thus, oxylipins, inhibit the release reaction, and activate adenylate cyclase, thereby preventing platelets from realizing their ability to decrease the blood fibrinolytic potential, whereas pro-aggregatory eicosanoids decrease the intensity of thrombolysis. The profibrinolytic effect of prostacyclin can also be mediated by another mechanism. Depression of fibrinolysis is known to be partly mediated by plasma carboxypeptidase-U-coenzyme which is activated by thrombin-induced proteolysis. Therefore, the PGI_2-mediated decrease in thrombin production can facilitate the activation of blood clot lysis [121].

The size of the vascular lumen is an important factor maintaining normal function of the blood coagulation system. It should be noted that it is exactly the physiological values of forces generated by mechanical interaction of blood flow with vascular walls that strongly determine the thromboresistance of endothelium. Even a small local decrease in vascular lumen sharply increases shear rates [122] to values that can activate cellular links of hemostasis, primarily platelets and leukocytes, with their further adhesion and aggregation [50, 102, 122]. These changes can proceed when the vascular wall conserves its anticoagulant properties [123]. On the other hand, an increase in the intensity of mechanical stimulation of the vascular intima is accompanied by activation of synthesis of vasodilator substance such as prostacyclin by endotheliocytes [14]. Release of PGI_2 into the bloodstream decreases the activity of blood cells, including platelets, and causes vasodilation. The latter response results in hemodynamic conditions that decrease the probability of procoagulant reactions. However, shear rate can be decreased abruptly by excess production of endogenous substances, especially in the presence of a functionally damaged vascular wall.

In this situation, activation of endothelial cells by certain agonists, such as pro-inflammatory cytokines, can increase the expression of tissue factor not only on the basal but also on the luminal surface of endotheliocytes with further activation of plasma hemostasis and fibrin deposition [109]. A low blood flow velocity probably provides optimal conditions for delivery of procoagulant factors to particular sites of the vascular wall and promotes intermolecular interactions [123, 124]. A sharp decrease in shear rates under physiological conditions decreases the rates of synthesis and liberation of vasodilators (including PGI_2 and NO) and increases the level of plasma endothelin [125, 126], which not only decreases platelet responses but primarily is a potent vasoconstrictor [127]. Endothelin initiates protein kinase C, which in turn activates phospholipase A_2, which results in liberation of arachidonic **acid** with further increase in PGI_2 production [128]. These data suggest that prostacyclin is a component of the system maintaining normal hemodynamic conditions.

Products of the lipoxygenase pathway of arachidonic **acid** metabolism are active regulators of vascular tone, and they can either increase or decrease the vascular lumen. Thus, low concentrations of 15-HETE induce vasodilation, whereas its high concentrations cause vasoconstriction. This vasodilation is probably related to activation of prostacyclin synthesis, whereas the 15-HETE-induced increase in the vascular wall tone is due to expression of thromboxane receptors on vascular smooth muscle cells [129, 130]. Cysteine-containing leukotrienes can influence the microvascular tone and induce a transitory arteriolar constriction [131]. In contrast to leukotrienes, lipoxins can cause arteriolar dilatation [132]. Arachidonic **acid** metabolites synthesized by the cytochrome P-450-dependent pathway are strong vasodilators [133]. Recent studies showed that after inhibition of NO synthase and cyclooxygenase, the vasodilator function of blood vessels is maintained by generation of an endothelial hyperpolarization factor [134] which can be a cytochrome P-540-dependent metabolite of arachidonic **acid** [134, 135]. The effects of prostacyclin on the vascular lumen is not restricted to its direct vasodilator effect. The ability of this eicosanoid to decrease the proliferative activity of the vascular wall smooth muscle cells is similarly important. This effect is caused by a decrease in liberation of vascular hyperplasia-inducing agents, such as platelet growth factor and platelet factor 4, from blood platelets; however, the antiproliferative effect of PGI_2 can be independent from platelet inactivation [136]. In contrast to PGI_2, TXA_2 stimulates hyperplasia of vascular walls [137]. There is evidence to suggest that 12-lipoxygenase metabolites of arachidonic **acid**, especially 12-HETE, may also be involved in regulation of proliferative processes. Mitogenic cell responses to angiotensin II and platelet growth factor were shown to require the activation of 12-lipoxygenase, which can act as a key factor of this process [138, 139].

Thus, numerous studies have shown that many oxylipins are much involved in regulation of blood coagulation; they maintain, in cooperation with other components of this system, a state of balance of procoagulant and anticoagulant processes under physiological conditions. Modulation of virtually all steps of hemostasis by metabolites of AA and other PUFA indicates that these substances display unique properties among all other biologically active substances affecting the mechanism of blood coagulation. Further studies of the possible physiological role of oxylipins in maintenance of the blood coagulation potential at an optimal level are extremely important because this research can expand our knowledge of normal physiology of hemostasis and have applied significance: it may find the causes and pathways of development of many severe diseases and show possible approaches to pharmacological and other therapeutic interventions to prevent and correct a number of

pathological states.

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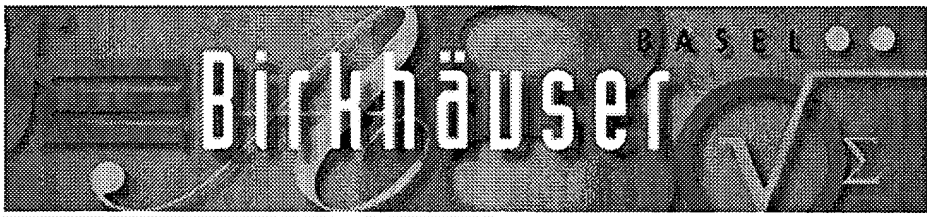

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Progress in Inflammation Research, (M. J. Parnham, Ed.)

Cutaneous essential fatty acids and hydroxy fatty acids: Modulation of inflammatory and hyperproliferative processes

By Vincent A. Ziboh

Summary

This paper details the biological significance of novel epidermal monohydroxy fatty acids catalyzed by 15-lipoxygenase (15-LO). **13-hydroxyoctadecadienoic** acid (13-HODE), derived from 18-carbon **linoleic** acid (LA), exerts a potent antiproliferative effect on cutaneous hyperproliferation, whereas the 20- and 22-carbon monohydroxy fatty acids: 15-hydrocyeicosatrienoic acid (15-HETrE), 15-hydroxyeicosatetraenoic acid (15-HETE), 15 hydroxyeicosapentaenoic acid (15-HEPE), and the 22-carbon 17-hydroxydocosahexaenoic acid (17-HDOHE), exert in vitro varying degrees of inhibitory effects on the generation of proinflammatory leukotriene B_4 (LTB_4) by polymorphonuclear (PMN) cells. The strongest effect is by 15-HETrE (a metabolite from dietary GLA). The mechanisms of the antiproliferative effect of 13-HODE is via the PKC/MAP-kinase signaling cascade. Taken together, these effects suggest that monohydroxy fatty acids generation by 15-LO could function in vivo to attenuate cutaneous inflammatory and proliferative disorders.

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Metabolism of polyunsaturated fatty acids by skin epidermal enzymes: generation of antiinflammatory and antiproliferative metabolites.

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In the skin epidermis, the metabolism of polyunsaturated fatty acids (PUFAs) is highly active. Dietary deficiency of **linoleic** acid (LA), the major 18-carbon n-6 PUFA in normal epidermis, results in a characteristic scaly skin disorder and excessive epidermal water loss. Because of the inability of normal skin epidermis to desaturate LA to gamma-linolenic acid, it is transformed by epidermal 15-lipoxygenase to mainly **13-hydroxyoctadecadienoic** acid, which functionally exerts antiproliferative properties in the tissue. In contrast, compared with LA, arachidonic acid (AA) is a relatively minor 20-carbon n-6 PUFA in the skin and is metabolized via the cyclooxygenase pathway, predominantly to the prostaglandins E(2), F(2)(alpha), and D(2). AA is also metabolized via the 15-lipoxygenase pathway, predominantly to 15-hydroxyeicosatetraenoic acid. At low concentrations, the prostaglandins function to modulate normal skin physiologic processes, whereas at high concentrations they induce inflammatory processes. PUFAs derived from other dietary oils are also transformed mainly into monohydroxy fatty acids. For instance, epidermal 15-lipoxygenase transforms dihomo-gamma-linolenic acid (20:3n-6) to 15-hydroxyeicosatrienoic acid, eicosapentaenoic acid (20:5n-3) to 15-hydroxyeicosapentaenoic acid, and docosahexaenoic acid (22:6n-3) to 17-hydroxydocosahexaenoic acid, respectively. These monohydroxy acids exhibit antiinflammatory properties in vitro. Thus, supplementation of diets with appropriate purified vegetable oils, fish oil, or both may generate local cutaneous antiinflammatory and antiproliferative metabolites which could serve as less toxic in vivo monotherapies or as adjuncts to standard therapeutic regimens for the management of inflammatory skin disorders.

Growth Differ 1998 Feb;9(2):147-5

Distinct functions of protein kinase Calpha and protein kinase Cbeta during retinoic acid-induced differentiation of F9 cells.

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As F9 embryonal carcinoma cells differentiate into parietal endoderm-like cells, expression of conventional protein kinase C (PKC) changes. Undifferentiated stem cells express PKCbeta but not PKCalpha, whereas differentiated parietal endoderm cells express PKCalpha but not PKCbeta. To determine whether changes in PKCalpha and/or PKCbeta expression control retinoic acid (RA)- and dibutyryl cyclic AMP-induced F9 cell differentiation, we established cell lines stably expressing PKCalpha, PKCbeta, antisense PKCalpha, or antisense PKCbeta RNAs. Constitutive expression of PKCalpha or inhibition of PKCbeta expression in F9 stem cells enhanced RA induced differentiation, both by increasing total expression and accelerating RA-induced expression of laminins A, B1, B2, and type IV collagen. In addition, expressing PKCbeta in a parietal endoderm cell line caused these cells to retrodifferentiate into stem cells. Based on these results, we conclude that PKCbeta and PKCalpha are key targets for RA-regulated gene expression, that PKCalpha plays an important, active role in inducing and maintaining the parietal endoderm phenotype, and that PKCbeta activity is incompatible with maintaining the differentiated state of these cells.

J Cell Physiol 1997 Sep;172(3):306-13

Retinoic acid induced growth arrest of human breast carcinoma cells requires protein kinase C alpha expression and activity.

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Retinoic acid inhibits proliferation of hormone-dependent, but not hormone-independent breast cancer cells. Retinoic acid-induced changes in cellular proliferation and differentiation are associated with disturbances in growth factor signaling and frequently with changes in protein kinase C expression. PKC delta, epsilon, and zeta are expressed in both hormone-dependent (T-47D) and hormone-independent (MDA-MB-231) cell lines. Retinoic acid arrested T-47D proliferation, induced PKC alpha expression and concomitantly repressed PKC zeta expression. The changes in PKC alpha and PKC zeta reflect retinoic acid-induced changes in mRNA. In contrast, retinoic acid had no effect on growth, or PKC expression in MDA-MB-231 cells. Growth arrest and the induction of PKC alpha, but not the reduction in PKC zeta, resulted from selective activation of RAR alpha. In total, these results support an important role for PKC alpha in mediating the anti-proliferative action of retinoids on human breast carcinoma cells.

Biochim Biophys Acta 1997 Nov 8;1349(1):67-71

A novel 15-hydroxyeicosatrienoic acid-substituted diacylglycerol (15-HETrE-DAG) selectively inhibits epidermal protein kinase C-beta.

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Diacylglycerol containing 15-hydroxyeicosatrienoic acid (15-HETrE-DAG) was biosynthesized and examined for modulation of epidermal protein kinase C (PKC) activity. 15-HETrE-DAG competitively inhibited diolein-activated total PKC activity in a dose-dependent manner and further, selectively inhibited epidermal PKC-beta activity.

Cell Growth Differ 1996 May;7(5):595-602

Retinoic acid-induced transition from protein kinase C beta to protein kinase C alpha in differentiated F9 cells: correlation with altered regulation of proto-oncogene expression by phorbol esters.

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Retinoic acid (RA) induced differentiation of F9 embryonal carcinoma cells is accompanied by changes in cellular responsiveness to extracellular signals. These changes include an increase in the AP1 transcription factor that is associated with the expression of differentiation markers (e.g., cytokeratin 18 and plasminogen activator). Since AP1 activity is a target for protein kinase C (PKC)-regulated changes in gene expression, we have examined the effects of RA on the expression and function of the PKC isozymes. F9 stem cells express PKC beta, delta, epsilon, and zeta. RA-induced differentiation to primitive endoderm led to a transition from PKC beta to PKC alpha expression. Additional treatment with dibutyryl cyclic AMP (dbcAMP), required for terminal differentiation into parietal endoderm, further increased PKC alpha expression and total PKC activity. RA and dbcAMP had negligible effects on the expression of PKC delta, epsilon, and zeta. The PKC beta to PKC alpha transition was specific for parietal endoderm; aggregation of RA-treated F9 cells induced visceral endoderm differentiation with elevated expression of PKC beta. The PKC activation with phorbol esters induced the expression of c-fos, c-jun, and junB proto-oncogenes in F9 stem cells. In the presence of either RA or RA and dbcAMP, phorbol ester treatment enhanced the expression of type IV collagen, a parietal endoderm marker. It also increased the expression of c-jun gene but not c-fos. The specific involvement of PKC beta in c-fos induction and PKC alpha in type IV collagen induction was confirmed in each PKC isozyme-transfected F9 cells.

Together, our data demonstrate that the RA-induced (and dbcAMP-induced) changes in conventional PKC expression alters gene expression during parietal endoderm formation.

J Nutr 1995 Nov;125(11):2741-50

Nutritional modulation of guinea pig skin hyperproliferation by essential fatty acid deficiency is associated with selective down regulation of protein kinase C-beta.

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In a previous study we demonstrated that **13-hydroxyoctadecadienoic** acid (13-HODE), a 15-lipoxygenase metabolite of **linoleic** acid is incorporated into epidermal phosphatidyl 4,5-bisphosphate (PtdIns 4,5-P2) and released as 13-HODE-containing-diacylglycerol (13-HODE-DAG). In vitro, 13-HODE-DAG was shown to selectively inhibit epidermal total protein kinase C (PKC-beta) activity. To determine whether these observations are relevant in vivo, guinea pigs were made essential fatty acid deficient (EFAD) by feeding them a basal diet supplemented with 4% hydrogenated coconut oil for 8 wk. Tissue levels of putative 13-HODE-DAG, protein kinase C (PKC) isozymes and tissue hyperproliferation were determined in the epidermal preparations from skin of control safflower oil-fed guinea pigs, those fed EFAD diet and those fed EFAD diet followed by the control diet for 2 wk. Our data revealed that cutaneous 13-HODE and 13-HODE-DAG were significantly lower in EFAD animals than in safflower-fed controls. These reductions were associated with both elevated epidermal hyperproliferation and elevated expressions and activities of PKC-alpha and beta-isozymes. Refeeding the animals with safflower oil for 2 wk replenished tissue levels of 13-HODE-DAG, which inversely correlated with the selective down regulation of PKC-beta expression and activity and the reversal of hyperproliferation. In contrast, although, the expression and activity of PKC-alpha was elevated in the epidermis of the EFAD guinea pigs, this elevated PKC-alpha expression was not down regulated after refeeding the safflower oil diet to the animals.

Biochem Biophys Res Commun 1994 May 30;201(1):257-65

13-Hydroxyoctadecadienoic acid reverses epidermal hyperproliferation via selective inhibition of protein kinase C-beta activity.

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13-Hydroxyoctadecadienoic acid (13-HODE) is a major lipoxygenase metabolite of **linoleic** acid in epidermis. Employing a docosahexaenoic acid (22:6n-3) induced model of hyperproliferative guinea pig epidermis, we demonstrated reversal of hyperproliferation by topical 13-HODE. To delineate a possible mechanism for 13-HODE effect, we demonstrated that topical 13-HODE was incorporated into 13-HODE-containing diacylglycerol (13HODE-DAG). This novel substituted-DAG which was markedly depleted in the hyperproliferative skin paralleled the increased activities of PKC-alpha and beta. Replenishment of the hyperproliferative epidermis with topical 13-HODE resulted in the accumulation of tissue 13HODE-DAG and the selective suppression of PKC-beta activity. These data taken together suggest that the generation of putative 13-HODE-DAG and the selective suppression of PKC-beta isozyme activity may play a role in modulating epidermal hyperproliferation.

J Lipid Res 1994 Feb;35(2):255-62

Incorporation of 13-hydroxyoctadecadienoic acid (13-HODE) into epidermal ceramides and phospholipids: phospholipase C-catalyzed release of novel 13-HODE-containing diacylglycerol.

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Ceramides and phospholipids constitute two important structural lipids of normal skin that are notably rich in polyunsaturated fatty acids. Although **linoleic** acid (LA) is high in the ceramides, the localization of its 15-lipoxygenase product, **13-hydroxyoctadecadienoic** acid (13-HODE) in the epidermis is unknown. In this study, we investigated the relative incorporation of [14C]LA and [14C]13-HODE into ceramides and phospholipids in isolated epidermal slices. Our data revealed minor incorporation of [14C]LA and [14C]13-HODE into ceramides. In contrast, both [14C]LA and [14C]13-HODE are markedly incorporated into phospholipids, particularly, phosphatidylcholine (PC) and phosphatidylinositol (PtdIns). The incorporation of 13-HODE into the PtdIns pool in particular prompted us to investigate into its fate in the signal transduction process and its possible incorporation into diacylglycerol. Our data revealed that 13-HODE is incorporated into epidermal phosphatidylinositol 4,5-bisphosphate (PtdIns4,5-P2) resulting in epidermal phospholipase C-catalyzed release into a novel 13-HODE-containing diacylglycerol (1-acyl-2-13-HODE-glycerol). The possibility now exists that this novel 13-HODE-containing diacylglycerol could function to modulate the activity of epidermal protein kinase C and hyperproliferation/differentiation.

J Lipid Res 1994 May;35(5):913-21

Expression of protein kinase C isozymes in guinea pig epidermis: selective inhibition of PKC-beta activity by 13-hydroxyoctadecadienoic acid-containing diacylglycerol.

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Prompted by the reversal of skin hyperproliferation to normal by 13-hydroxyoctadecadienoic acid (13-HODE), a 15-lipoxygenase metabolite of linoleic acid, we investigated a possible mechanism for this antiproliferative action. To address this we first demonstrated that 13-HODE is incorporated into epidermal phosphatidyl 4,5-bisphosphate (PtdIns4,5-P2) and released as 13-HODE-containing diacylglycerol by epidermal phospholipase C. Secondly, we tested the possibility whether this putative 13-HODE-containing DAG (13HODE-DAG) could exert a modulatory effect on epidermal protein kinase C (PKC) activity which previously has been associated with skin hyperproliferation. Unlabeled 13HODE-DAG was generated from 13-HODE-containing phosphatidylcholine after phospholipase C hydrolytic cleavage. The effects of the 13HODE-DAG were determined on: i) total epidermal PKC activity; ii) diolein-activated PKC activity; and iii) the two identified epidermal PKC-isozymes (PKC-beta and PKC-alpha). Our data revealed over a twofold activation of total basal PKC activity by diolein. In contrast, replacement of diolein (1,2-dioleoylglycerol) with 13HODE-DAG (1-palmitoyl,2-13HODE-glycerol) in the incubation mixture exerted no effect on total basal PKC activity. In an another experiment, 13HODE-DAG inhibited diolein-activated PKC activity in a dose-dependent manner. To determine whether the effects of 13HODE-DAG are selective, we tested its effects on DEAE-Sephacel-purified and Western blot-confirmed PKC isozymes. Our data revealed that 13HODE-DAG selectively inhibited the activity of PKC-beta isozyme, while exerting negligible effect on the PKC-alpha isozyme. This selective inhibitory effect of 13HODE-DAG on a major epidermal PKC isozyme activity suggests that 13HODE-containing DAG seemingly can modulate epidermal PKC activity, which purportedly is associated with epidermal hyperproliferation.